Breast Cancer Research

RESEARCH

Open Access

# Pharmacovigilance study of adverse reactions of anti-HER-2 drugs for the treatment of HER-2-positive breast cancer based on the FAERS database

Jinming Han[1†], Xiaohan Zhai[1†], Xufeng Tao[1], Yunming Li[1], Ziqi Zhao[2], Zhan Yu[1], Deshi Dong[1], Shilei Yang[1] and Linlin Lv[1*]

## Abstract

**Objective** There are three categories of drugs that treat human epidermal growth factor receptor type 2 (HER-2) positive breast cancer: monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), and tyrosine kinase inhibitors (TKIs). The purpose of this study is to analyze and compare the adverse reactions of three classes of anti-HER-2 drugs to various body systems in patients based on the FDA Adverse Event Reporting System (FAERS).

**Methods** All data reports were extracted from the FAERS between 2004 and 2024. Data mining of adverse events associated with anti-HER-2 drugs was carried out using disproportionality analysis. A multivariate logistic regression analysis was conducted to explore the risk factors associated with AEs leading to hospitalization.

**Results** A total of 47,799 patients were screened for the three classes of drugs, among which ADC drugs caused the largest proportion of deaths. MAb has the strongest ADR signals associated with "cardiac disorders". Moreover, trastuzumab was associated with a greater risk of cardiotoxicity. Logistic regression analysis revealed that the treatment with mAbs should be wary of serious adverse reactions in "infections and infestations" and "metabolism and nutrition disorders". Moreover, "endocrine disorders" were the factor associated with the highest risk of prolonged hospitalization due to trastuzumab deruxtecan (T-DXd). The safety of tucatinib among TKI drugs is greater than that of other drugs.

**Conclusion** In general, from the perspective of the effects of the three classes of drugs on the various body systems of patients, we should focus on mAb-associated "cardiac disorders", ADC-associated "hepatobiliary disorders", "respiratory, thoracic and mediastinal disorders", and TKI-associated "gastrointestinal disorders.

**Keywords** HER-2-positive breast cancer, Monoclonal antibodies, Tyrosine kinase inhibitors, Antibody-drug conjugates, Pharmacovigilance, Adverse events, FAERS

†Jinming Han and Xiaohan Zhai are the co-first authors and contributed equally to this work.

*Correspondence:
Linlin Lv
lvlinlinyu@163.com

[1]Department of Pharmacy, First Affiliated Hospital of Dalian Medical University, Dalian 116024, China
[2]Department of Breast Surgery, First Affiliated Hospital of Dalian Medical University, Dalian, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

## Introduction

Breast cancer is the leading cause of cancer death in women. According to the latest data from the United States in 2023, breast cancer accounts for more than 32% of new cases of female cancer, which has attracted global attention [1]. Breast cancer is a heterogeneous disease that can be classified into four distinct molecular subtypes based on cell surface receptor expression: luminal A, luminal B, human epidermal growth factor receptor type 2 (HER-2), and triple-negative breast cancer (TNBC). Each subtype has unique characteristics, epidemiology, response to treatment, and prognosis [2–4]. Among these subtypes, HER-2-positive breast cancer is characterized primarily by HER-2 overexpression and is considered the second most invasive subtype [3, 4]. Approximately 20–30% of breast cancers demonstrate HER-2 amplification and/or overexpression. The overexpression of the HER-2 receptor is associated with a poor prognosis for patients and shorter overall survival [5, 6]. Therefore, HER-2 receptors are the best oncologic target for treatment interventions, management, and targeted therapy development for HER-2-positive breast cancer. Currently, HER-2 pathway-blocking drugs used worldwide for the treatment of HER-2-positive breast cancer include three categories: monoclonal antibodies (margetuximab, pertuzumab, trastuzumab), antibody-drug conjugates (trastuzumab deruxtecan, trastuzumab emtansine), and tyrosine kinase inhibitors (lapatinib, neratinib, pyrotinib, tucatinib) [7].

With the wide application of these different kinds of HER-2-targeting drugs, their adverse drug reactions have also aroused widespread concern. For example, anti-HER-2 monoclonal antibodies can cause cardiotoxicity, with an incidence ranging from 0.7–12% [8, 9], and approximately 40% of patients may experience allergic reactions such as fever, chills, hypotension, dyspnea, and rash during or after infusion [10, 11]. The incidence of diarrhea associated with pertuzumab has reached 72% [12, 13]. Some reports have shown that trastuzumab, trastuzumab deruxtecan, and lapatinib are correlated with interstitial lung disease, resulting in an overall adverse reaction incidence rate of 2.4%, whereas the incidence rate of interstitial lung disease caused by trastuzumab shows a high incidence rate of 21.4% [14]. In addition, tyrosine kinase inhibitor therapy can also lead to hepatotoxicity, diarrhea, neutropenia, leukopenia, and severe skin reactions, such as palmar-plantar erythrodysesthesia (PPE) (in more than 25% of patients) [15, 16]. Therefore, it is necessary to conduct an in-depth analysis and evaluation of adverse reactions associated with HER-2-targeted drugs for the treatment of HER-2-positive breast cancer.

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting system for adverse events (AEs) established by the US Food and Drug Administration (FDA) and is designed to support postmarketing monitoring plans for drugs and therapeutic biologic products [17]. The FAERS is the world's largest pharmacovigilance tool and encompasses adverse reaction reports from various regions worldwide. It is used to collect and analyze adverse events related to drug use, including adverse drug reactions(ADRs), drug misuse, drug abuse, and drug overdose, etc. Based on real-world raw data from the FAERS database, this study conducted a comprehensive analysis of adverse reactions associated with three types of HER-2-targeted drugs for HER-2-positive breast cancer by using disproportionation methods to identify risk signals in three types of drug adverse reaction reports and compared their differences. In addition, the risk factors associated with the occurrence of adverse reactions and possible causal relationships were evaluated.

The significance of this project lies in providing a scientific basis for safe drug utilization, guiding health care professionals and patients in making rational medication choices, avoiding unnecessary risks, and ensuring safe medication for patients by reducing adverse drug reactions through pharmacovigilance research, all of which can save medical costs, reduce medical insurance expenditures, improve patient satisfaction with medical services and drug quality, and contribute to social economic benefits and overall social productivity.

## Methods

### Data source

This study acquired original data from Q1 of 2004 to Q3 of 2024 from the FAERS database downloaded from the FDA public database. We acquired 83 quarterly American Standard Code for Information Interchange (ASCII) data packages, which contain seven parts: patient demographic and management information, drug information, adverse event information, patient medical outcomes, reporting sources, start and end of drug treatment information, and drug indications. Additionally, this study used the preferred term (PT) from the Medical Dictionary for Regulatory Activities (MedDRA version 27.0) to code adverse events in the FAERS database and list primary system organ classes (SOCs) corresponding to these PTs. Our study contains 27 SOCs, and we used MedDRA (version 27.0) to classify adverse events in each report to the corresponding SOC levels where a PT can be linked to more than one SOC because of MedDRA's multiaxiality. Within the significant safety signal for each SOC, we reported counts of each adverse event found using PTs to describe the most frequent adverse events in each SOC for every drug [18, 19].

### Study design

There are three types of anti-HER-2 drugs targeted to treat HER-2-positive breast cancer, including monoclonal antibodies (margetuximab, pertuzumab, trastuzumab), antibody-drug conjugates (trastuzumab deruxtecan (T-DXd), trastuzumab emtansine (T-DM1)), and tyrosine kinase inhibitors (lapatinib, neratinib, pyrotinib, tucatinib). During the screening process, we established the inclusion criteria for patients' indications to include the field "breast cancer". Since the data in the FAERS database were collected using spontaneous reports, we conducted this process in strict accordance with the guidance document from the FDA website for data cleaning and deleted some duplicate reports or reports that were withdrawn/deleted from the database. According to the method of removing duplicate reports recommended by the FDA, we selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table and sorted them by CASEID, FDA_DT, and PRIMARYID. We selected the reports with the same CASEID and retained the largest FDA_DT value. For those reports with the same CASEID and FDA_DT, we retained the largest PRIMARYID value.

The FAERS database uses the field "DRUGNAME" to signify drug names and the field "PROD_AI" to note the product components, and each patient (report) will have only "the first Suspect (Primary Suspect Drug, PS)" of drugs; therefore, we only considered the first suspected patients with target drugs. Patients were included in the target drug population if the patient's first suspected drug was the target drug of the study. For each patient, we retrieved demographic characteristics (sex, age), administrative information (reporter region, reporter year), and reaction details (time to ADR onset, severity, and outcomes). During the data mining process, we searched using preferred terms (PTs), counted records according to individual safety reports (ISRs) and employed disproportionality analysis (DPA) methods to identify risk signals in adverse reaction reports.

### Statistical analysis

This study is based on disproportionality analysis to detect safety signals for drugs. We used the reporting odds ratio (ROR) and proportional reporting ratio (PRR) to measure the association ratio of the observed frequency in the exposed population compared to that in the nonexposed population [20, 21]. Furthermore, we used a multi-item gamma Poisson shrinker (MGPS) [22] and a Bayesian confidence propagation neural network (BCPNN) [23] to confirm our findings and decrease false-positive safety signals. These methods are based on a four-grid table (Supplemental Table 1) to analyze the association between drug exposure and the AE (signal). The formulas of proportional imbalance methods are shown in Supplemental Table 2. A signal was determined if $a \geq 3$, 95% CI lower threshold exceeded 1, the PRR was $>2$ with a corresponding $\chi^2 > 4$, and the IC 95% CI lower value was $>0$. In this study, if the PRR or ROR was $\geq 2.0$ and the 95% confidence interval values exceeded 1.0 (null value), we considered the safety signals to be significant [24]. The AE signal was stronger when the ROR and the PRR were greater and indicated a stronger statistical relationship between the target drug and the target AE. All analyses were performed using SAS9.4, and GraphPad Prism (*v 9.1*) was used to construct the figures. In addition, SAS 9.4 (a pharmacovigilance tool) was used to analyze and conduct retrospective pharmacovigilance analysis of adverse event information about the target drug [25, 26].

Through regression analysis, we analyzed the risk of hospitalization due to SOCs associated with the AEs of anti-HER-2 drugs. First, one-way logistic regression was performed. The 27 SOCs associated with the occurrence of adverse reactions were taken as independent variables, and the outcome of patients' adverse reactions (whether hospitalization occurred) was considered the response variable. Second, multivariate logistic regression was performed on SOCs with $p < 0.05$ in the univariate regression to identify which factors might contribute to an increased risk of hospitalization. To determine the accuracy of the regression model, receiver operating characteristic (ROC) analysis was performed. The area under the curve (AUC) is a measure of the ROC curve, and an AUC $>0.7$ usually indicates that the model has good predictive power [27].

## Results

### Patient characteristics

The FAERS database has recorded 18,278,243 cases (after deletion) from the first quarter of 2004 to the third quarter of 2024, including 47,799 reports for target anti-HER-2 drugs, with 5584, 23,625, 4573, 3558, 7225, 1338, and 1896 attributed to pertuzumab, trastuzumab, T-DXd, T-DM1, lapatinib, neratinib and tucatinib, respectively, as the primary suspect. We summarized patients' demographics in these 47,799 reports for descriptive analysis, which are outlined in the form of charts (Table 1). Among all the drugs used in this study, females (85.64%) were more often affected than males. This may be closely related to the characteristics of breast cancer itself. Except for a considerable number of reports that did not specify the age of patients, reports of patients receiving anti-HER-2 drugs tended to be approximately 45–64 years of age. Notably, lapatinib (43.52%) in the TKI class was associated with a greater incidence of adverse reactions in patients aged 45–64 years than the other six anti-HER-2 drugs. With respect to the distribution of the time to ADR onset across all drugs, with the exception of nonspecific or abnormal values, 7 anti-HER-2 drugs

**Table 1** Demographics in patients with Anti-HER2 drugs related adverse events

| Characteristic | mAb | | ADC | | TKI | | |
|---|---|---|---|---|---|---|---|
| | Pertuzumab | Trastuzumab | T-DXd | T-DM1 | Lapatinib | Neratinib | Tucatinib |
| **N** | 5584 | 23,625 | 4573 | 3558 | 7225 | 1338 | 1896 |
| **Report Region** | | | | | | | |
| Asia | 2148(38.47) | 5786(24.49) | 648(14.17) | 1134(31.87) | 1107(15.32) | 12(0.90) | 26(1.37) |
| Europe | 1463(26.20) | 8541(36.15) | 992(21.69) | 957(26.90) | 1281(17.73) | 86(6.43) | 313(16.51) |
| South America | 123(2.20) | 1071(4.53) | 73(1.60) | 123(3.46) | 130(1.80) | 52(3.89) | 0(0.00) |
| Africa | 71(1.27) | 340(1.44) | 7(0.15) | 23(0.65) | 47(0.65) | 1(0.07) | 0(0.00) |
| Oceania | 68(1.22) | 351(1.49) | 24(0.52) | 67(1.88) | 64(0.89) | 2(0.15) | 5(0.26) |
| North America | 1709(30.61) | 7171(30.35) | 2828(61.84) | 1253(35.22) | 4431(61.33) | 1173(87.67) | 1551(81.80) |
| NS | 2(0.04) | 365(1.54) | 1(0.02) | 1(0.03) | 165(2.28) | 12(0.90) | 1(0.05) |
| **Sex** | | | | | | | |
| Female | 5094(91.22) | 19,715(83.45) | 4070(89.00) | 3288(92.41) | 6864(95.00) | 64(4.78) | 1840(97.05) |
| Male | 55(0.98) | 222(0.94) | 59(1.29) | 44(1.24) | 61(0.84) | 0(0.00) | 23(1.21) |
| NS | 435(7.79) | 3688(15.61) | 444(9.71) | 226(6.35) | 300(4.15) | 1274(95.22) | 33(1.74) |
| **Age** | | | | | | | |
| < 18 | 0(0.00) | 9(0.04) | 3(0.07) | 2(0.06) | 2(0.03) | 0(0.00) | 1(0.05) |
| 18–44 | 734(13.14) | 2774(11.74) | 256(5.60) | 389(10.93) | 772(10.69) | 14(1.05) | 137(7.23) |
| 45–64 | 2139(38.31) | 7690(32.55) | 1016(22.22) | 1336(37.55) | 3144(43.52) | 40(2.99) | 386(20.36) |
| 65–74 | 682(12.21) | 2399(10.15) | 442(9.67) | 429(12.06) | 941(13.02) | 3(0.22) | 142(7.49) |
| ≥ 75 | 272(4.87) | 1003(4.25) | 234(5.12) | 150(4.22) | 360(4.98) | 3(0.22) | 37(1.95) |
| NS | 1757(31.46) | 9750(41.27) | 2622(57.34) | 1252(35.19) | 2006(27.76) | 1278(95.52) | 1193(62.92) |
| **Time to ADR onset** | | | | | | | |
| 0-30d | 1631(29.21) | 4257(18.02) | 506(11.06) | 558(15.68) | 1928(26.69) | 269(20.10) | 154(8.12) |
| 31-60d | 217(3.89) | 673(2.85) | 122(2.67) | 121(3.40) | 403(5.58) | 39(2.91) | 45(2.37) |
| 61-90d | 164(2.94) | 514(2.18) | 99(2.16) | 125(3.51) | 305(4.22) | 20(1.49) | 21(1.11) |
| 91-120d | 131(2.35) | 392(1.66) | 64(1.40) | 77(2.16) | 197(2.73) | 8(0.60) | 12(0.63) |
| 121-150d | 75(1.34) | 317(1.34) | 57(1.25) | 48(1.35) | 152(2.10) | 7(0.52) | 11(0.58) |
| 151-180d | 53(0.95) | 227(0.96) | 37(0.81) | 45(1.26) | 103(1.43) | 1(0.07) | 10(0.53) |
| 181-360d | 130(2.33) | 844(3.57) | 123(2.69) | 155(4.36) | 312(4.32) | 22(1.64) | 29(1.53) |
| 360d< | 203(3.64) | 1233(5.22) | 62(1.36) | 193(5.42) | 329(4.55) | 9(0.67) | 20(1.05) |
| NS(< 0) | 2980(53.37) | 15,168(64.20) | 3503(76.60) | 2236(62.84) | 3496(48.39) | 963(71.97) | 1594(84.07) |
| **Outcome** | | | | | | | |
| LT | 282(5.05) | 896(3.79) | 179(3.91) | 128(3.60) | 197(2.73) | 5(0.37) | 7(0.37) |
| HO | 2032(36.39) | 6031(25.53) | 1175(25.69) | 1144(32.15) | 1886(26.10) | 331(24.74) | 665(35.07) |
| DS | 77(1.38) | 457(1.93) | 43(0.94) | 66(1.85) | 129(1.79) | 4(0.30) | 13(0.69) |
| DE | 524(9.38) | 2843(12.03) | 1091(23.86) | 527(14.81) | 1134(15.70) | 166(12.41) | 219(11.55) |
| CA | 2(0.04) | 32(0.14) | 2(0.04) | 0(0.00) | 2(0.03) | 0(0.00) | 3(0.16) |
| RI | 0(0.00) | 56(0.24) | 4(0.09) | 6(0.17) | 3(0.04) | 1(0.07) | 0(0.00) |
| OT | 2509(44.93) | 13,144(55.64) | 2250(49.20) | 1671(46.96) | 2263(31.32) | 320(23.92) | 671(35.39) |
| **Severe ADR** | 4799(85.94) | 20,190(85.46) | 3525(77.08) | 2984(83.87) | 4706(65.13) | 669(50.00) | 1225(64.61) |

LT, Life-Threatening; HO, Hospitalization - Initial or Prolonged; DS, Disability; DE, Death; CA, Congenital Anomaly; RI, Required Intervention to Prevent Permanent Impairment/Damage; OT, Other;

were associated with a duration of approximately 0–30 days. For mAb drugs, pertuzumab (29.21%) was associated with a greater incidence of ADRs within 0–30 days than trastuzumab (18.02%). The proportion of T-DM1 and T-DXd in ADC drugs was similar. However, the occurrence rate of ADRs caused by TKI drugs from 0 to 30 days varied greatly. Specifically, lapatinib occurred in 26.69%, neratinib in 20.10%, and tucatinib in 8.12% of the patients. The majority of the outcomes for the patients in the reports were HO (hospitalization–initial or prolonged), including pertuzumab as a mAb (36.39%), which had the highest proportion, followed by tucatinib as a TKI (35.07%). However, the proportion of HO resulting from T-DM1 treatment (32.15%) is relatively higher. Moreover, in terms of the overall severity of all reports, mAb drugs led to the most severe ADRs (pertuzumab at 85.94%, trastuzumab at 85.46%). The ADC drugs were associated with the second most severe incidence of ADRs (T-DXd at 77.08%, T-DM1 at 83.87%). The incidence of severe ADRs associated with TKI drugs is

relatively low, and the lowest incidence of adverse reactions associated with neratinib is 50.00%.

Summarizing the adverse event profiles that have occurred with the three anti-HER-2 agents since their marketing approval, the number of adverse events reported (patient dimension) is shown in Fig. 1. Before 2012, the ADRs were mainly for lapatinib and trastuzumab, and ADRs associated with lapatinib were more than that for trastuzumab from 2007 to 2011. In the past 10 years (2012–2023), mAb drugs, especially trastuzumab, have been associated with more ADRs. The number of reports of TKI drugs is relatively small, and neratinib has the least number of ADR reports. We found that the number of reports of lapatinib tended to decrease after 2015. With respect to ADC drugs, T-DXd has had a greater number of ADR reports than T-DM1 since its introduction. In 2023, T-DXd (1601 patients) had the second highest number of adverse reactions reported among the seven drugs after trastuzumab (2366 patients).

The FAERS database includes adverse event reports from different geographic regions of the world, including North America, Europe, Asia, South America, Oceania, and Africa. Based on the geographic region of the patient, we generated a heatmap of the number of patients associated with three anti-HER-2 drugs. As shown in the heatmap in Fig. 2, trastuzumab had the highest number of reported cases in Europe (8,541 cases), followed by North America (7,171 cases) and Asia (5,786 cases). The lowest number of ADR cases was reported in Africa. Among the ADC drugs, T-DXd had a greater number of cases in North America (2,828 cases), whereas T-DXd and T-DM1 had a lower number of cases in South America, Oceania, and Africa. Among the TKI drugs, lapatinib had a relatively high number of reported cases on six continents. Overall, the number of ADR cases reported was relatively greater in regions with relatively developed economies.

To evaluate and analyze the outcome of ADRs in patients with HER-2-related breast cancer treated with anti-HER-2 drugs, reports of drug-related death (DE) were selected for statistical analysis, and the results are shown in Fig. 3. Among the three classes of drugs, ADC drugs caused the largest proportion of deaths, followed by TKI drugs. Among the patients receiving ADC drugs, T-DXd-related mortality was 23.86%, which was also the highest among those receiving all seven drugs. Among the TKI drugs, lapatinib was associated with a mortality rate of 15.70%, whereas neratinib and tucatinib were associated with similar rates (12.41% and 11.55%, respectively). It is worth noting that, trastuzumab had the highest number of ADRs, but its mortality rate is only 12.03%. Among all the seven drugs, pertuzumab had the lowest mortality rate, at 9.38%.

### Descriptive analysis of the AE reports

The circular proportion graph was constructed according to the number of PT reports of AEs caused by different drugs and is shown in Fig. 4. The number of PTs with AEs caused by trastuzumab was as high as 75,323 reports at 49.63%, followed by lapatinib with 22,664 reports at 14.93% and pertuzumab with 15,009 reports at 9.89%.

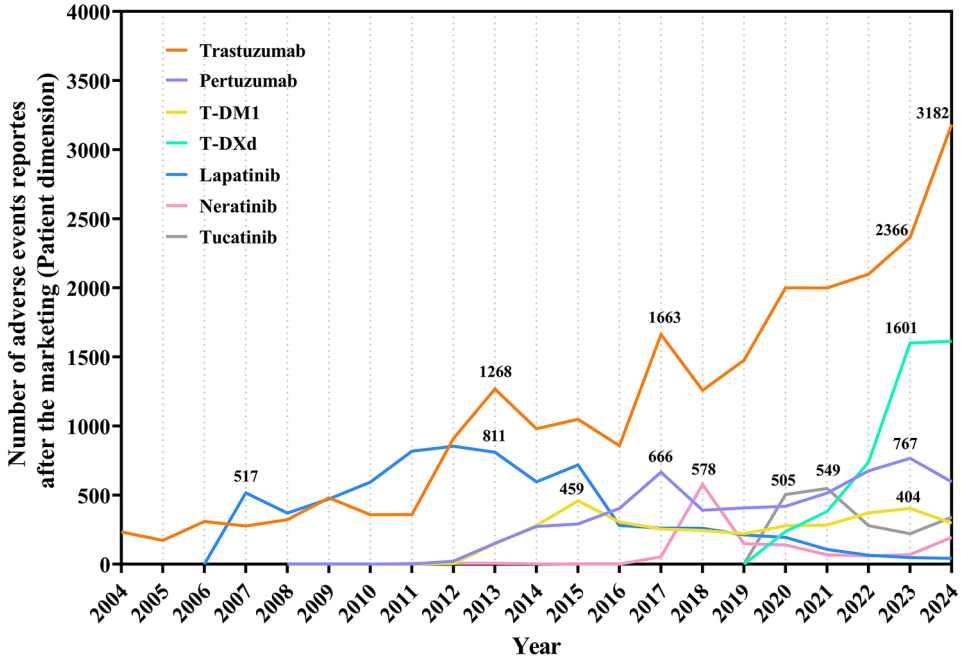



**Fig. 1** The number of adverse events of three anti-HER-2 drugs since their marketing approval (patient dimension)

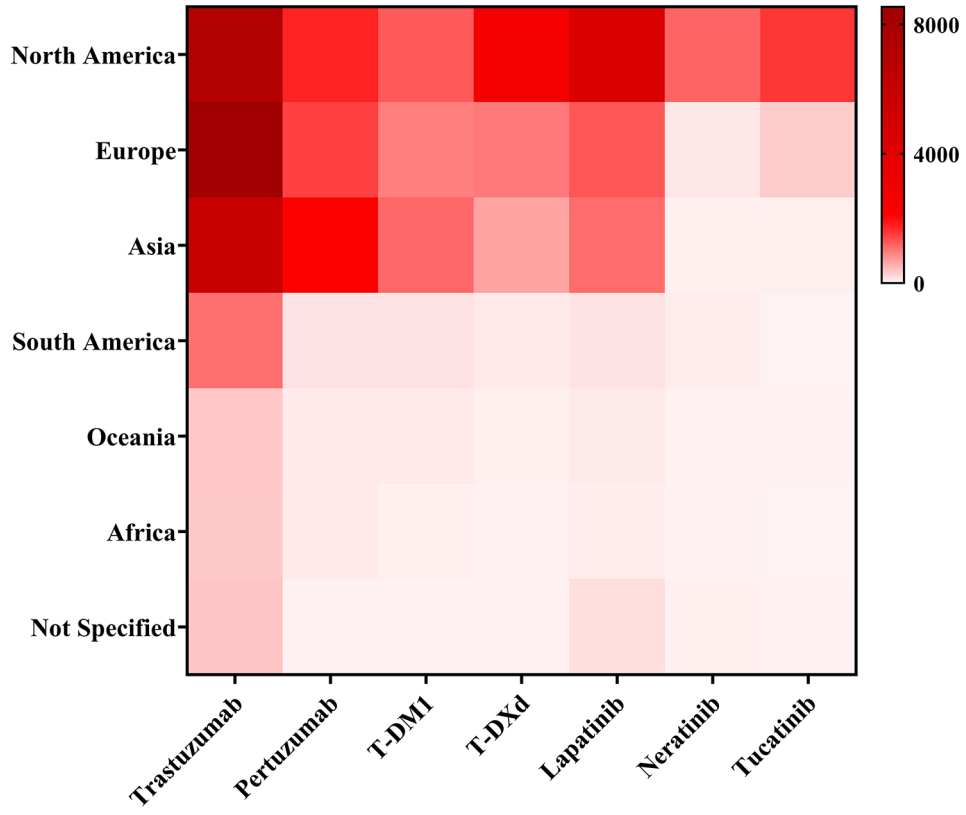
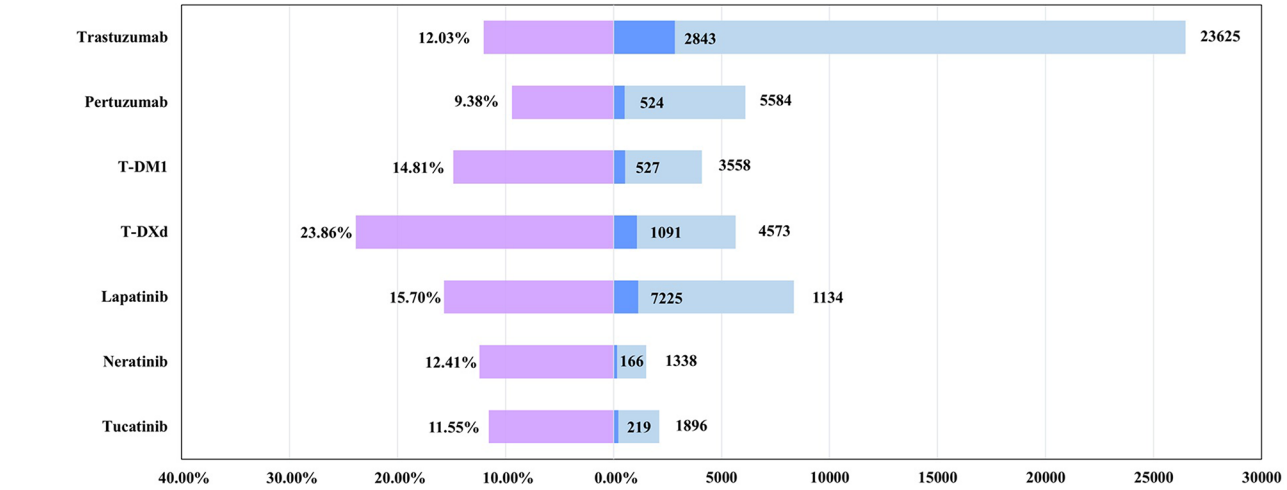



**Fig. 2** Heat map of the number of adverse reactions associated with three anti-HER-2 drugs based on the geographic region of the patient




| | Trastuzumab | Pertuzumab | T-DM1 | T-DXd | Lapatinib | Neratinib | Tucatinib |
|---|---|---|---|---|---|---|---|
| Number of death | 2843 | 524 | 527 | 1091 | 1134 | 166 | 219 |
| Number of cases | 23625 | 5584 | 3558 | 4573 | 7225 | 1338 | 1896 |
| Fatality proportion(%) | 12.03% | 9.38% | 14.81% | 23.86% | 15.70% | 12.41% | 11.55% |

**Fig. 3** Proportion of deaths among adverse outcomes associated with three anti-HER-2 agents

The number of PTs of T-DM1, T-DXd, and tucatinib were similar, at 6.91%, 8.06%, and 6.36%, respectively. Moreover, we found that among the TKIs, neratinib had the lowest number of PTs with AEs with 6,398 reports (4.22%).

In accordance with the "polyaxial" characteristics of the MedDRA, these drug-related PT signals were dispersed to 27 different SOCs. Through analysis of the original data of the target drugs, we found that the ADRs of the three classes of anti-HER-2 drugs had great differences

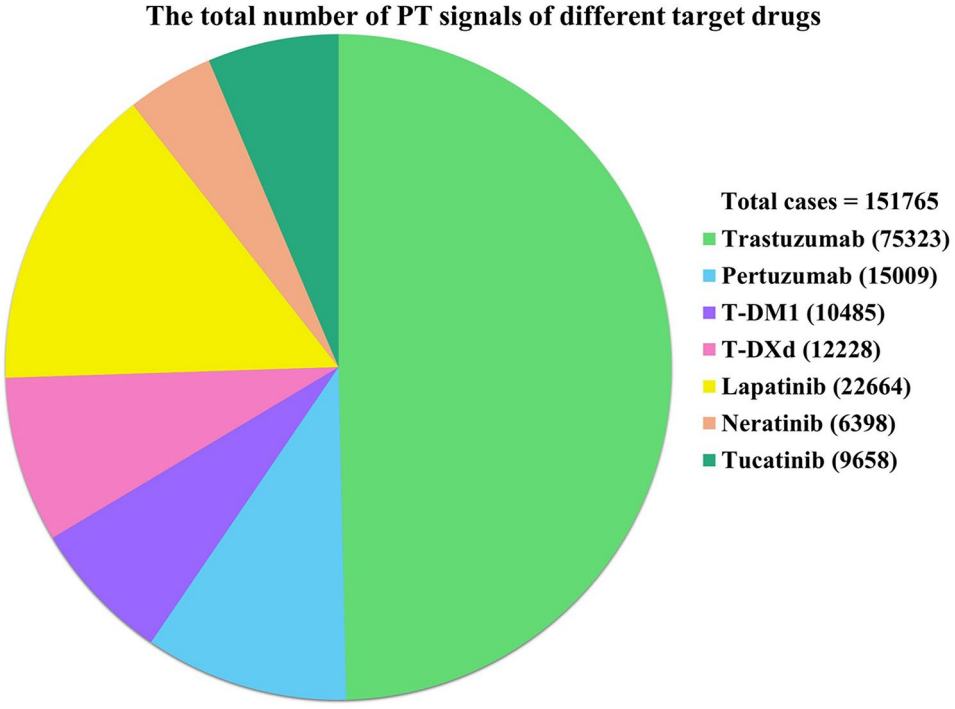



**Fig. 4** The circular proportion graph was constructed according to the number of PT reports of AEs caused by three different anti-HER-2 agents

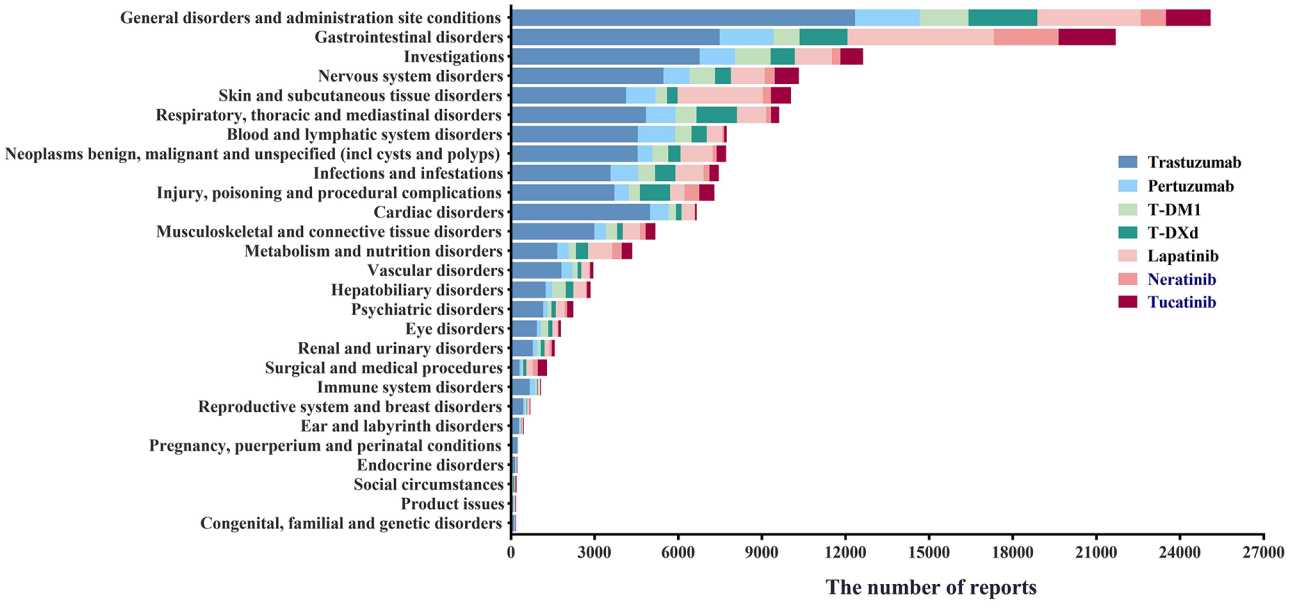



**Fig. 5** The number of adverse events reported by three anti-HER2 drugs in 27 SOC

in the distribution under different SOCs. As shown in Fig. 5, among the 27 SOCs, ADRs related to "general disorders and administration site conditions" accounted for the highest proportion, followed by "gastrointestinal diseases". The ADRs associated with SOC, such as "congenital, familial and genetic disorders", "product issues", "social circumstances", "endocrine disorders" and "pregnancy, puerperium and perinatal conditions" constitute a small proportion.

We can intuitively see that mAb had the highest proportion of ADRs in total, followed by TKI, which was consistent with the results of the total number of PT signals for adverse reactions mentioned in Fig. 4. In terms of the ADRs associated with "general disorders and administration site conditions", trastuzumab accounted

for the highest proportion, followed by lapatinib. However, among "gastrointestinal disorders", lapatinib caused more ADR reports than "general disorders and administration site conditions". However, among the seven drugs, trastuzumab was still the drug with the highest incidence of "gastrointestinal disorders". According to the classification of drugs, the number of ADR reports of "gastrointestinal disorders" caused by TKI drugs was relatively high. Furthermore, in addition to the general disorders and gastrointestinal disorders, the number of adverse reactions categorized under "respiratory, thoracic, and mediastinal disorders" induced by ADCs is relatively higher compared to those caused by other standard-of-care treatments.

### Signal analysis of adverse reactions associated with three different anti-HER-2 drugs

Through disproportionation analysis, we evaluated the signals of ROR, PRR, IC, and EBGM and their 95% confidence intervals (CIs) for three classes of anti-HER-2 drugs under different SOCs. Four adverse reaction signals on the 27 system organ class levels of mAb drugs are shown in Table 2. Trastuzumab had the strongest ADR signals associated with "cardiac disorders" and "pregnancy, puerperium and perinatal conditions". The RORs of which were 3.51 (95% CI: 3.40–3.63) and 3.37 (95% CI: 2.92–3.90); Both the PRR, IC and EBGM also showed significant ADR signals. In addition, pertuzumab showed a relatively strong ADR signal in "blood and lymphatic system disorders", "cardiac disorders" and "immune system disorders". We plotted the distribution RORs of these significant SOCs using forest plots, as shown in Fig. 6. The forest plot results further revealed that among the two mAb drugs, trastuzumab had a greater frequency and stronger signal of ADRs in patients with "cardiac disorders".

Similarly, four adverse reaction signals on the 27 SOC levels of ADC drugs are shown in Table 3. T-DM1 shows significant ADR signals in "hepatobiliary disorders" only (ROR: 3.09, PRR: 3.00, IC: 1.56, EBGM: 2.94). The forest plots also show consistent results (Fig. 6). Meanwhile, T-DXd had a significant ADR signal in "respiratory, thoracic and mediastinal disorders" (ROR: 2.33, PRR: 2.17, IC: 1.10, EBGM: 2.14), and "injury, poisoning and procedural complications" (ROR: 2.07, PRR: 1.98, IC: 0.97, EBGM: 1.96). So, we found that T-DM1 did not generate a significant signal related to the same SOC with T-DXd.

Through analysis of the ADR signals of the three drugs in the TKI class, we found that all three drugs showed significant signals in "gastrointestinal disorders", and the signal of neratinib was the strongest (ROR: 4.70, PRR: 3.36, IC: 1.73, EBGM: 3.31), followed by lapatinib (ROR: 2.50, PRR: 2.15, IC: 1.07, EBGM: 2.10) (Table 4). Neratinib also had significant ADR effects on "surgical and medical procedures" and "metabolism and nutrition disorders". Tucatinib also had significant ADR effects on "surgical and medical procedures". The results of the forest plots revealed that tucatinib had a stronger effect than neratinib in Surgical and medical procedures (Fig. 6).

### Comparison of safety signals of anti-HER-2 drugs in different SOCs

Based on the results above, we identified three SOCs with significant ADR signals among the three types of anti-HER-2 drugs. To further compare the characteristics of PTs corresponding to each type of drug under the SOC, we selected PTs with ROR greater than 2 and the ADR reports number of which ranks among the top 5. Simultaneously, by combining the corresponding $\chi^2$ value and the number of ADR reports for each PT, a bubble chart was plotted to compare the position of each PT, thereby analyzing the intensity of the signal. The larger the dots in the chart, the greater the number of ADR reports for the corresponding PT of the drug. Moreover, when the position of the position of the point in the graph is high and far both algorithms indicate a stronger signal of adverse events. As the results in Fig. 7 show, the signal of diarrhea under the SOC of "gastrointestinal disorders" for the three TKI drugs was the strongest. Among the three drugs, lapatinib (ROR = 5.40, $\chi^2$=6506.34) and neratinib (ROR = 7.32, $\chi^2$=3897.63) had the highest risk of diarrhea, especially lapatinib, which had the largest number of reports (2240 cases). Comparatively speaking, the signal of tucatinib has the weakest signal in diarrhea (ROR = 3.63, $\chi^2$=1191.57). In addition to diarrhea, neratinib is also at a significant risk of constipation and nausea. Moreover, among the three types of TKI drugs, neratinib (ROR = 3.40, $\chi^2$=625.74) has the highest risk of causing nausea and the most significant signal intensity. For lapatinib, the risk and signal of vomiting are stronger than those of nausea.

Similarly, we found that both neratinib and tucatinib produced strong ADR signals in the SOC of "surgical operation and medical treatment". Moreover, tucatinib has the highest risk and the strongest signal of hospice care (ROR = 24.77, $\chi^2$=1304.21). As shown in Fig. 7, the risk of hospitalization associated with tucatinib is comparably similar to that of neratinib, but the number of cases reported is marginally higher(107 cases). Furthermore, we also noticed that the risks of emergency care (ROR = 58.77, $\chi^2$=456.27) and breast reconstruction (ROR = 15.40, $\chi^2$=61.36) related to neratinib are relatively high.

The two mAb drugs have different PT signals under the SOC of patients with "cardiac disorders". The results indicate that the risk of cardiotoxicity occurring in patients taking tratuzumab (ROR: 12.71, $\chi^2$: 3321.87) is the highest. Meanwhile, the risk of such cardiotoxicity is much

**Table 2** Four adverse reaction signals on the 27 system organ class levels of mAb drugs

| System organ class | Trastuzumab | | | | Pertuzumab | | | |
|---|---|---|---|---|---|---|---|---|
| | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) |
| Eye disorders | 0.85(0.80–0.91) | 0.85(0.80–0.91) | -0.21(-0.31–-0.11) | 0.86(0.81–0.92) | 0.67(0.57–0.79) | 0.67(0.57–0.79) | -0.57(-0.80–-0.32) | 0.68(0.57–0.80) |
| Blood and lymphatic system disorders | 1.30(1.26–1.34) | 1.28(1.25–1.32) | 0.33(0.29–0.38) | 1.26(1.22–1.30) | 1.96(1.86–2.08) | 1.88(1.78–1.98) | 0.89(0.81–0.97) | 1.86(1.75–1.96) |
| Vascular disorders | 1.13(1.08–1.19) | 1.13(1.08–1.19) | 0.16(0.09–0.23) | 1.12(1.07–1.18) | 1.24(1.13–1.38) | 1.24(1.12–1.36) | 0.30(0.15–0.45) | 1.23(1.12–1.36) |
| Cardiac disorders | 3.51(3.40–3.63) | 3.34(3.24–3.45) | 1.51(1.47–1.56) | 2.86(2.76–2.95) | 1.98(1.83–2.15) | 1.94(1.80–2.09) | 0.94(0.82–1.05) | 1.91(1.77–2.07) |
| Gastrointestinal disorders | 0.89(0.86–0.91) | 0.90(0.88–0.92) | -0.14(-0.18–-0.11) | 0.90(0.88–0.93) | 1.21(1.15–1.27) | 1.18(1.13–1.23) | 0.24(0.17–0.31) | 1.18(1.12–1.24) |
| Reproductive system and breast disorders | 0.91(0.83–1.01) | 0.91(0.83–1.01) | -0.12(-0.26–0.02) | 0.92(0.83–1.01) | 0.72(0.57–0.92) | 0.73(0.57–0.92) | -0.46(-0.80–-0.11) | 0.73(0.58–0.92) |
| Renal and urinary disorders | 0.83(0.78–0.90) | 0.84(0.78–0.90) | -0.24(-0.35–-0.14) | 0.85(0.79–0.91) | 0.86(0.74–1.01) | 0.86(0.74–1.01) | -0.21(-0.44–0.02) | 0.87(0.74–1.01) |
| Social circumstances | 0.16(0.12–0.21) | 0.16(0.12–0.21) | -2.54(-2.90–-2.14) | 0.17(0.13–0.22) | 0.15(0.08–0.28) | 0.15(0.08–0.28) | -2.73(-3.48–-1.74) | 0.15(0.08–0.28) |
| Pregnancy, puerperium and perinatal conditions | 3.37(2.92–3.90) | 3.36(2.91–3.89) | 1.52(1.30–1.72) | 2.87(2.48–3.32) | 0.87(0.51–1.47) | 0.87(0.51–1.47) | -0.20(-0.94–0.56) | 0.87(0.51–1.47) |
| General disorders and administration site conditions | 1.14(1.12–1.16) | 1.12(1.10–1.14) | 0.15(0.12–0.18) | 1.11(1.09–1.13) | 1.06(1.01–1.10) | 1.05(1.01–1.09) | 0.07(0.00–0.13) | 1.05(1.00–1.09) |
| Skin and subcutaneous tissue disorders | 0.53(0.51–0.54) | 0.55(0.54–0.57) | -0.81(-0.86–-0.76) | 0.57(0.55–0.59) | 0.71(0.66–0.75) | 0.73(0.69–0.77) | -0.45(-0.54–-0.36) | 0.73(0.69–0.78) |
| Endocrine disorders | 0.67(0.57–0.79) | 0.67(0.57–0.79) | -0.54(-0.78–-0.29) | 0.69(0.58–0.81) | 0.30(0.17–0.51) | 0.30(0.17–0.51) | -1.73(-2.43–-0.88) | 0.30(0.17–0.52) |
| Immune system disorders | 1.31(1.21–1.42) | 1.31(1.21–1.42) | 0.36(0.24–0.47) | 1.28(1.18–1.39) | 1.88(1.63–2.17) | 1.87(1.62–2.15) | 0.88(0.67–1.09) | 1.84(1.60–2.13) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1.03(1.00–1.06) | 1.03(1.00–1.06) | 0.04(-0.01–0.09) | 1.03(1.00–1.06) | 0.58(0.53–0.64) | 0.60(0.55–0.65) | -0.74(-0.86–-0.61) | 0.60(0.55–0.66) |
| Psychiatric disorders | 0.37(0.35–0.39) | 0.38(0.36–0.40) | -1.33(-1.41–-1.24) | 0.40(0.38–0.42) | 0.28(0.24–0.33) | 0.29(0.25–0.34) | -1.78(-2.00–-1.55) | 0.29(0.25–0.34) |
| Respiratory, thoracic and mediastinal disorders | 1.19(1.15–1.23) | 1.18(1.14–1.21) | 0.22(0.17–0.26) | 1.16(1.13–1.20) | 1.31(1.23–1.40) | 1.29(1.22–1.37) | 0.36(0.27–0.46) | 1.29(1.21–1.37) |
| Congenital, familial and genetic disorders | 1.28(1.07–1.54) | 1.28(1.07–1.54) | 0.33(0.06–0.59) | 1.26(1.05–1.51) | 0.35(0.17–0.73) | 0.35(0.17–0.74) | -1.50(-2.40–-0.36) | 0.35(0.17–0.74) |
| Surgical and medical procedures | 0.44(0.40–0.50) | 0.45(0.40–0.50) | -1.11(-1.27–-0.94) | 0.46(0.41–0.52) | 0.61(0.49–0.76) | 0.62(0.50–0.76) | -0.69(-1.00–-0.37) | 0.62(0.50–0.77) |
| Musculoskeletal and connective tissue disorders | 0.67(0.64–0.69) | 0.68(0.65–0.70) | -0.52(-0.58–-0.47) | 0.69(0.67–0.72) | 0.47(0.43–0.52) | 0.49(0.44–0.53) | -1.03(-1.17–-0.88) | 0.49(0.44–0.54) |
| Injury, poisoning and procedural complications | 1.10(1.06–1.14) | 1.09(1.06–1.13) | 0.12(0.07–0.17) | 1.09(1.05–1.12) | 0.75(0.68–0.81) | 0.75(0.69–0.82) | -0.40(-0.53–-0.27) | 0.76(0.69–0.83) |
| Nervous system disorders | 1.21(1.17–1.24) | 1.19(1.16–1.22) | 0.23(0.19–0.27) | 1.17(1.14–1.21) | 1.01(0.94–1.08) | 1.01(0.95–1.07) | 0.01(-0.09–0.11) | 1.01(0.94–1.08) |
| Investigations | 1.05(1.02–1.08) | 1.04(1.02–1.07) | 0.06(0.02–0.09) | 1.04(1.01–1.07) | 0.98(0.92–1.04) | 0.98(0.93–1.04) | -0.03(-0.11–0.06) | 0.98(0.93–1.04) |
| Infections and infestations | 1.10(1.06–1.14) | 1.10(1.06–1.13) | 0.12(0.07–0.17) | 1.09(1.05–1.13) | 1.55(1.46–1.66) | 1.52(1.43–1.61) | 0.59(0.49–0.69) | 1.51(1.41–1.61) |
| Hepatobiliary disorders | 1.08(1.02–1.15) | 1.08(1.02–1.14) | 0.10(0.02–0.19) | 1.07(1.01–1.14) | 1.04(0.92–1.19) | 1.04(0.92–1.18) | 0.06(-0.13–0.25) | 1.04(0.92–1.18) |
| Ear and labyrinth disorders | 1.13(1.00–1.27) | 1.12(1.00–1.27) | 0.16(-0.02–0.33) | 1.11(0.99–1.26) | 0.57(0.40–0.82) | 0.58(0.40–0.82) | -0.79(-1.29–-0.25) | 0.58(0.40–0.83) |

**Table 2** (continued)

| System organ class | Trastuzumab | | | | Pertuzumab | | | |
|---|---|---|---|---|---|---|---|---|
| | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) |
| Metabolism and nutrition disorders | 0.80(0.76–0.84) | 0.80(0.77–0.84) | -0.29(-0.37–-0.22) | 0.82(0.78–0.86) | 1.03(0.93–1.13) | 1.03(0.93–1.13) | 0.04(-0.11–0.18) | 1.02(0.93–1.13) |
| Product issues | 0.38(0.30–0.48) | 0.38(0.30–0.48) | -1.33(-1.66–-0.96) | 0.40(0.31–0.51) | 0.34(0.20–0.61) | 0.34(0.20–0.61) | -1.52(-2.25–-0.65) | 0.35(0.20–0.61) |

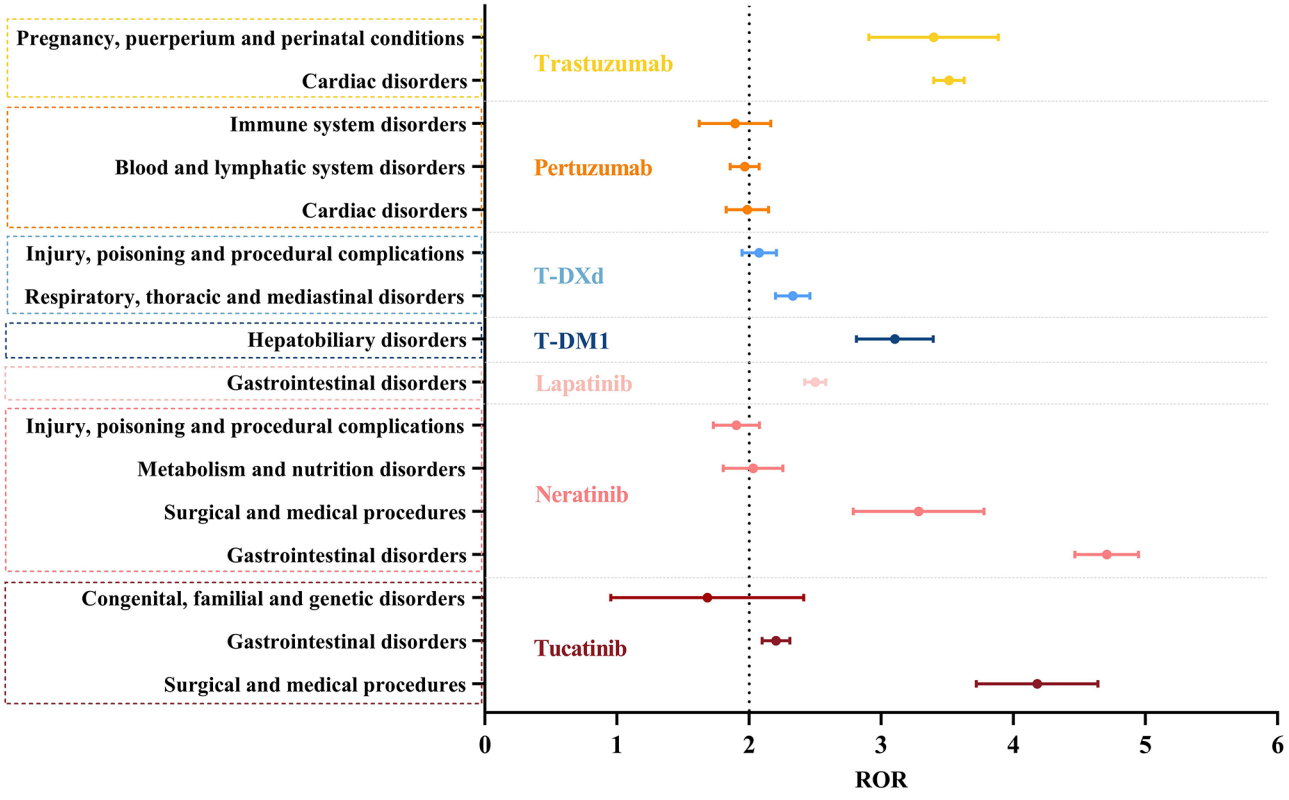



**Fig. 6** SOC with significant adverse reaction signals in three anti-HER-2 agents

higher than that of pertuzumab (ROR: 3.93, $\chi^2$: 140.02). Whereas left ventricular dysfunction (ROR: 6.57, $\chi^2$: 658.17) is second only to cardiotoxicity in tratuzumab. Compared with other PTs, pertuzumab had the highest risk of cardiac dysfunction (ROR: 8.89, $\chi^2$: 247.00).

### Analysis of the risk of hospitalization due to serious adverse events induced by three types of anti-HER-2 drugs

To compare and evaluate the risk of serious adverse events resulting in hospitalization for three anti-HER-2 drugs, we performed a regression analysis of the SOCs associated with these drugs and whether patients were hospitalized. First, we conducted univariate regression analysis with the outcome of patients' adverse reactions (whether hospitalization occurred) was considered the response variable, and 27 SOCs associated with the occurrence of adverse reactions were taken as independent variables among the three classes of drugs. According to the results of the univariate regression analysis, SOC with a p value less than 0.05 was selected for multivariate logistic regression analysis. The AUC values of the seven drugs in the regression analysis were all greater than 0.7, indicating that the regression model had good predictive ability.

As shown in Fig. 8, trastuzumab had 10 SOCs that increase the risk of hospitalization, including "infections and infestations (OR: 2.81)", "surgical and medical procedures (OR: 2.60)", "respiratory, thoracic and mediastinal disorders (OR: 2.14)", "metabolism and nutrition disorders (OR: 1.68)", "gastrointestinal disorders (OR: 1.61)", and so on. Pertuzumab had 5 SOCs that increased the risk of hospitalization, including "infections and infestations (OR: 3.28)", "metabolism and nutrition disorders (OR: 2.62)", "blood and lymphatic system disorders (OR: 2.26)", "renal and urinary disorders (OR: 1.65)", "gastrointestinal disorders (OR: 1.54)", "psychiatric disorders (OR: 1.24)".

**Table 3** Four adverse reaction signals on the 27 system organ class levels of ADC drugs

| System organ class | T-DM1 | | | | T-DXd | | | |
|---|---|---|---|---|---|---|---|---|
| | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) |
| Eye disorders | 1.75(1.55–1.98) | 1.73(1.53–1.96) | 0.78(0.60–0.96) | 1.72(1.52–1.95) | 0.87(0.74–1.02) | 0.87(0.74–1.02) | -0.20(-0.44–0.03) | 0.87(0.74–1.02) |
| Blood and lymphatic system disorders | 1.18(1.08–1.28) | 1.17(1.08–1.26) | 0.22(0.10–0.34) | 1.17(1.07–1.27) | 0.93(0.85–1.01) | 0.93(0.86–1.01) | -0.10(-0.22–0.03) | 0.94(0.86–1.02) |
| Vascular disorders | 0.78(0.67–0.91) | 0.78(0.68–0.91) | -0.35(-0.57–-0.13) | 0.79(0.68–0.91) | 0.52(0.44–0.62) | 0.53(0.45–0.62) | -0.92(-1.16–-0.67) | 0.53(0.45–0.63) |
| Cardiac disorders | 1.10(0.97–1.24) | 1.09(0.97–1.23) | 0.13(-0.05–0.31) | 1.09(0.97–1.24) | 0.68(0.59–0.79) | 0.69(0.60–0.79) | -0.53(-0.74–-0.32) | 0.69(0.60–0.80) |
| Gastrointestinal disorders | 0.78(0.73–0.84) | 0.80(0.75–0.85) | -0.32(-0.42–-0.22) | 0.80(0.75–0.86) | 1.33(1.26–1.40) | 1.28(1.23–1.34) | 0.35(0.28–0.43) | 1.28(1.21–1.35) |
| Reproductive system and breast disorders | 0.68(0.51–0.91) | 0.68(0.51–0.91) | -0.54(-0.96–-0.11) | 0.69(0.51–0.92) | 0.24(0.15–0.38) | 0.24(0.15–0.38) | -2.04(-2.63–-1.34) | 0.24(0.15–0.38) |
| Renal and urinary disorders | 0.95(0.80–1.14) | 0.95(0.80–1.14) | -0.07(-0.33–0.19) | 0.95(0.80–1.14) | 0.91(0.77–1.08) | 0.91(0.77–1.07) | -0.14(-0.38–0.11) | 0.91(0.77–1.08) |
| Social circumstances | 0.17(0.09–0.34) | 0.17(0.09–0.34) | -2.53(-3.36–-1.43) | 0.17(0.09–0.35) | 0.87(0.65–1.16) | 0.87(0.65–1.16) | -0.20(-0.62–0.22) | 0.87(0.65–1.16) |
| Pregnancy, puerperium and perinatal conditions | 0.53(0.24–1.18) | 0.53(0.24–1.18) | -0.91(-1.90–0.28) | 0.53(0.24–1.19) | 0.00(0.00–0.00) | 0.00(0.00–0.00) | 0.00(0.00–0.00) | 0.00(0.00–0.00) |
| General disorders and administration site conditions | 1.15(1.10–1.22) | 1.13(1.08–1.18) | 0.17(0.10–0.25) | 1.13(1.07–1.19) | 1.47(1.40–1.53) | 1.37(1.32–1.42) | 0.45(0.38–0.51) | 1.37(1.31–1.43) |
| Skin and subcutaneous tissue disorders | 0.38(0.35–0.42) | 0.41(0.37–0.45) | -1.28(-1.43–-1.14) | 0.41(0.37–0.45) | 0.30(0.27–0.33) | 0.32(0.29–0.35) | -1.63(-1.78–-1.48) | 0.32(0.29–0.36) |
| Endocrine disorders | 0.49(0.30–0.82) | 0.50(0.30–0.82) | -1.01(-1.68–-0.24) | 0.50(0.30–0.83) | 0.42(0.25–0.70) | 0.42(0.26–0.70) | -1.23(-1.90–-0.45) | 0.43(0.26–0.71) |
| Immune system disorders | 0.83(0.64–1.07) | 0.83(0.64–1.07) | -0.27(-0.63–0.10) | 0.83(0.64–1.07) | 0.38(0.27–0.54) | 0.38(0.27–0.54) | -1.38(-1.85–-0.85) | 0.38(0.27–0.54) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.91(0.84–0.99) | 0.92(0.85–0.99) | -0.12(-0.25–0.00) | 0.92(0.84–1.00) | 0.59(0.54–0.65) | 0.61(0.55–0.67) | -0.71(-0.85–-0.57) | 0.61(0.55–0.67) |
| Psychiatric disorders | 0.31(0.26–0.37) | 0.32(0.27–0.37) | -1.65(-1.90–-1.39) | 0.32(0.27–0.38) | 0.33(0.28–0.38) | 0.34(0.29–0.39) | -1.56(-1.79–-1.33) | 0.34(0.29–0.40) |
| Respiratory, thoracic and mediastinal disorders | 1.31(1.22–1.41) | 1.29(1.20–1.38) | 0.36(0.25–0.47) | 1.29(1.19–1.39) | 2.33(2.20–2.46) | 2.17(2.07–2.28) | 1.10(1.02–1.18) | 2.14(2.03–2.27) |
| Congenital, familial and genetic disorders | 0.65(0.34–1.25) | 0.65(0.34–1.25) | -0.62(-1.49–0.35) | 0.65(0.34–1.25) | 0.31(0.13–0.74) | 0.31(0.13–0.74) | -1.69(-2.70–-0.33) | 0.31(0.13–0.75) |
| Surgical and medical procedures | 0.45(0.33–0.61) | 0.45(0.33–0.61) | -1.14(-1.56–-0.68) | 0.45(0.33–0.61) | 1.13(0.95–1.36) | 1.13(0.95–1.35) | 0.18(-0.09–0.44) | 1.13(0.94–1.35) |
| Musculoskeletal and connective tissue disorders | 0.64(0.58–0.71) | 0.66(0.59–0.72) | -0.60(-0.75–-0.45) | 0.66(0.59–0.73) | 0.28(0.24–0.32) | 0.29(0.26–0.33) | -1.76(-1.96–-1.55) | 0.29(0.26–0.34) |
| Injury, poisoning and procedural complications | 0.82(0.74–0.91) | 0.83(0.75–0.91) | -0.27(-0.42–-0.12) | 0.83(0.75–0.92) | 2.07(1.95–2.21) | 1.98(1.87–2.10) | 0.97(0.87–1.06) | 1.96(1.84–2.08) |
| Nervous system disorders | 1.45(1.35–1.55) | 1.41(1.33–1.50) | 0.49(0.39–0.59) | 1.41(1.31–1.51) | 0.74(0.68–0.81) | 0.75(0.69–0.82) | -0.40(-0.53–-0.28) | 0.76(0.69–0.82) |
| Investigations | 1.47(1.38–1.55) | 1.41(1.34–1.48) | 0.49(0.40–0.57) | 1.40(1.32–1.49) | 0.81(0.75–0.87) | 0.82(0.77–0.88) | -0.28(-0.38–-0.18) | 0.82(0.77–0.88) |
| Infections and infestations | 1.35(1.24–1.47) | 1.33(1.23–1.44) | 0.41(0.29–0.53) | 1.33(1.22–1.44) | 1.39(1.29–1.50) | 1.37(1.28–1.47) | 0.45(0.34–0.56) | 1.36(1.27–1.47) |
| Hepatobiliary disorders | 3.09(2.82–3.40) | 3.00(2.74–3.28) | 1.56(1.41–1.69) | 2.94(2.68–3.23) | 1.46(1.29–1.65) | 1.45(1.29–1.63) | 0.53(0.35–0.70) | 1.44(1.28–1.63) |
| Ear and labyrinth disorders | 1.05(0.76–1.45) | 1.05(0.76–1.44) | 0.07(-0.40–0.53) | 1.05(0.76–1.45) | 0.42(0.27–0.67) | 0.42(0.27–0.67) | -1.23(-1.85–-0.52) | 0.43(0.27–0.68) |

**Table 3** (continued)

| System organ class | T-DM1 | | | | T-DXd | | | |
|---|---|---|---|---|---|---|---|---|
| | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) | ROR(95%CI) | PRR(95%CI) | IC(95%CI) | EBGM(95%CI) |
| Metabolism and nutrition disorders | 0.91(0.80–1.03) | 0.91(0.80–1.02) | -0.14(-0.32–0.04) | 0.91(0.80–1.03) | 1.34(1.22–1.47) | 1.33(1.21–1.46) | 0.40(0.26–0.54) | 1.32(1.20–1.46) |
| Product issues | 0.70(0.44–1.13) | 0.70(0.44–1.13) | -0.50(-1.16–0.20) | 0.71(0.44–1.14) | 0.57(0.35–0.93) | 0.57(0.35–0.93) | -0.81(-1.48–-0.07) | 0.57(0.35–0.93) |

Among the ADC drugs, T-DM1 had 5 SOCs that increase the risk of hospitalization, including "infections and infestations (OR: 4.49)", "renal and urinary disorders(OR: 2.27)", "metabolism and nutrition disorders (OR: 1.89)", "cardiac disorders (OR: 1.47)", "blood and lymphatic system disorders (OR: 1.27)" (Fig. 9). T-DXd had 10 SOCs that increased the risk of hospitalization, including "endocrine disorders (OR: 22.7)", "infections and infestations (OR: 3.73)", "surgical and medical procedures (OR: 3.10)", "metabolism and nutrition disorders (OR: 2.85)", "vascular disorders (OR: 2.59)" and so on. From the forest map, we can observe that "endocrine disorders" induced by T-DXd represent the most significant risk factor for patient hospitalization.

The results for the TKI drugs are shown in Fig. 10. Lapatinib showed that 11 SOCs, including "infections and infestations (OR: 4.59)", "surgical and medical procedures (OR: 3.87)", "blood and lymphatic system disorders (OR: 3.83)", "metabolism and nutrition disorders (OR: 3.72)", "renal and urinary disorders (OR: 2.86)", "reproductive system and breast disorders (OR: 2.22)", "vascular disorders (OR: 2.11)", "cardiac disorders (OR: 1.90)", "hepatobiliary disorders (OR: 1.82)", "respiratory, thoracic and mediastinal disorders (OR: 1.80)" and "nervous system disorders (OR: 1.31)" increased the risk of hospitalization for patients. The results of neratinib treatment revealed that 8 SOCs increased the risk of hospitalization for patients. Among these factors, the risk of hospitalization for patients due to "surgical and medical procedures (OR: 12.48)" is the highest, followed by "cardiac disorders (OR: 3.81)" and "hepatobiliary disorders (OR: 3.77)". Compared with others, tucatinib is associated with relatively fewer risk factors for hospitalization of patients. There are 6 SOCs that may increase the risk of hospitalization, including "surgical and medical procedures (OR: 6.65)", "infections and infestations (OR: 5.59)", "endocrine disorders (OR: 5.18)", "respiratory, thoracic and mediastinal disorders (OR: 2.21)", "metabolism and nutrition disorders (OR: 1.76)", "nervous system disorders (OR: 1.45)".

## Discussion

With the increasing incidence and mortality of breast cancer and the expanding use of anticancer drugs, the management of adverse events associated with anti-breast cancer drugs has become a major challenge and requires further research. Using real-world data, we compared the adverse effects of three classes of anti-HER-2 targeted drugs for the treatment of HER-2 breast cancer for the first time, thus discovering the impact of these anti-HER-2 drugs on various body systems in patients more comprehensively and extensively.

From the perspective of the overall characteristics of patients, most of the sources of adverse reaction reports were concentrated in areas with relatively high social development levels. Some epidemiological studies have shown that there is a correlation between the level of national economic development and the incidence and mortality of breast cancer [28]. In regions with a low level of development, the incidence and mortality rates of breast cancer are relatively high [29]. This situation clearly demonstrates that these underdeveloped areas attach insufficient importance to the diagnosis and treatment of breast cancer, as well as drug vigilance. Hence, efforts should be made to enhance the understanding of drug safety, conduct publicity and education, and promote the extensive application of drug vigilance research in clinical practice. This will help reduce the occurrence of disease aggravation and complications resulting from adverse drug reactions and interactions, especially for antitumor drugs.

In this study, the collated data revealed that the largest proportion of patients who experienced ADRs after using anti-HER-2 drugs were aged 45–64 years. The number of ADR reports was also greater in patients aged 45–64 years, but the number of ADRs after medication was lower in patients aged 18–44 years and the lowest in those younger than 18 years. This may be related to the age of onset of breast cancer itself and the hormone levels of female patients. Studies have shown that late menopause is believed to be achieved after the age of 54 years and increases the risk of breast cancer by twofold compared with that of menopause achieved before the age of 45 years [30, 31]. The meta-analysis also revealed that women who had not reached menopause had a greater risk of developing breast cancer than postmenopausal women of the same age. Women in late menopause are also predisposed to the development of steroid-expressing breast cancer [31].

Currently, HER-2 pathway-blocking drugs used worldwide to treat HER-2-positive breast cancer include mAbs, ADCs, and TKI agents. Trastuzumab and pertuzumab are the most commonly used monoclonal drugs

**Table 4** Four adverse reaction signals on the 27 system organ class levels of TKI drugs

| System organ class | Tucatinib | | | | Neratinib | | | | Lapatinib | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) |
| Eye disorders | 0.66 (0.54– 0.81) | 0.66 (0.54– 0.81) | -0.59 (-0.88– -0.28) | 0.67 (0.54– 0.82) | 0.43 (0.32– 0.59) | 0.44 (0.32– 0.59) | -1.19 (-1.63– -0.72) | 0.44 (0.32– 0.60) | 0.53 (0.46– 0.62) | 0.53 (0.46– 0.62) | -0.89 (-1.10– -0.66) | 0.54 (0.47–0.63) |
| Blood and lymphatic system disorders | 0.20 (0.17– 0.25) | 0.21 (0.17– 0.26) | -2.24 (-2.52– -1.94) | 0.21 (0.17– 0.26) | 0.18 (0.14– 0.23) | 0.18 (0.14– 0.24) | -2.43 (-2.79– -2.03) | 0.19 (0.14– 0.24) | 0.49 (0.45– 0.54) | 0.51 (0.47– 0.55) | -0.96 (-1.09– -0.84) | 0.51 (0.47–0.56) |
| Vascular disorders | 0.53 (0.44– 0.64) | 0.53 (0.44– 0.64) | -0.90 (-1.17– -0.62) | 0.53 (0.44– 0.64) | 0.36 (0.27– 0.47) | 0.36 (0.27– 0.48) | -1.46 (-1.85– -1.04) | 0.36 (0.28– 0.48) | 0.54 (0.48– 0.61) | 0.55 (0.48– 0.62) | -0.86 (-1.03– -0.68) | 0.55 (0.49–0.62) |
| Cardiac disorders | 0.28 (0.22– 0.36) | 0.28 (0.22– 0.36) | -1.81 (-2.15– -1.43) | 0.29 (0.22– 0.37) | 0.12 (0.08– 0.20) | 0.13 (0.08– 0.20) | -2.97 (-3.55– -2.25) | 0.13 (0.08– 0.20) | 0.90 (0.82– 0.99) | 0.90 (0.82– 0.99) | -0.14 (-0.28– -0.01) | 0.90 (0.82–0.99) |
| Gastrointestinal disorders | 2.20 (2.10– 2.31) | 1.95 (1.87– 2.02) | 0.95 (0.88– 1.02) | 1.93 (1.84– 2.03) | 4.70 (4.47– 4.95) | 3.36 (3.25– 3.47) | 1.73 (1.65– 1.79) | 3.31 (3.14– 3.48) | 2.50 (2.42– 2.58) | 2.15 (2.10– 2.21) | 1.07 (1.02– 1.11) | 2.10 (2.03–2.17) |
| Reproductive system and breast disorders | 0.29 (0.18– 0.46) | 0.29 (0.18– 0.46) | -1.78 (-2.39– -1.06) | 0.29 (0.18– 0.46) | 0.49 (0.31– 0.75) | 0.49 (0.31– 0.75) | -1.03 (-1.63– -0.37) | 0.49 (0.31– 0.76) | 0.54 (0.43– 0.68) | 0.54 (0.43– 0.68) | -0.87 (-1.19– -0.53) | 0.55 (0.44–0.69) |
| Renal and urinary disorders | 0.94 (0.78– 1.13) | 0.94 (0.78– 1.13) | -0.09 (-0.36– 0.19) | 0.94 (0.78– 1.14) | 0.98 (0.78– 1.22) | 0.98 (0.78– 1.22) | -0.03 (-0.36– 0.30) | 0.98 (0.78– 1.22) | 0.64 (0.55– 0.74) | 0.64 (0.56– 0.75) | -0.62 (-0.84– -0.4) | 0.65 (0.56–0.75) |
| Social circumstances | 0.99 (0.73– 1.34) | 0.99 (0.73– 1.33) | -0.02 (-0.46– 0.42) | 0.99 (0.73– 1.34) | 0.56 (0.35– 0.92) | 0.57 (0.35– 0.92) | -0.82 (-1.48– -0.08) | 0.57 (0.35– 0.93) | 0.20 (0.13– 0.31) | 0.20 (0.13– 0.31) | -2.27 (-2.83– -1.60) | 0.21 (0.14–0.32) |
| Pregnancy, puerperium and perinatal conditions | 0.10 (0.01– 0.68) | 0.10 (0.01– 0.68) | -3.37 (-4.55– -0.47) | 0.10 (0.01– 0.69) | 0.58 (0.22– 1.55) | 0.58 (0.22– 1.55) | -0.78 (-1.95– 0.64) | 0.58 (0.22– 1.55) | 0.17 (0.06– 0.45) | 0.17 (0.06– 0.45) | -2.54 (-3.57– -0.98) | 0.17 (0.06–0.46) |
| General disorders and administration site conditions | 1.15 (1.09– 1.21) | 1.12 (1.07– 1.18) | 0.17 (0.09– 0.24) | 1.12 (1.06– 1.18) | 0.95 (0.88– 1.02) | 0.95 (0.90– 1.01) | -0.07 (-0.17– 0.04) | 0.96 (0.89– 1.03) | 1.12 (1.08– 1.16) | 1.10 (1.07– 1.13) | 0.14 (0.08– 0.19) | 1.10 (1.06–1.14) |
| Skin and subcutaneous tissue disorders | 0.76 (0.71– 0.82) | 0.78 (0.73– 0.84) | -0.36 (-0.47– -0.24) | 0.78 (0.72– 0.84) | 0.44 (0.39– 0.50) | 0.47 (0.42– 0.52) | -1.10 (-1.27– -0.92) | 0.47 (0.41– 0.53) | 1.45 (1.40– 1.51) | 1.39 (1.35– 1.44) | 0.47 (0.41– 0.52) | 1.38 (1.33–1.43) |
| Endocrine disorders | 0.54 (0.32– 0.89) | 0.54 (0.32– 0.89) | -0.89 (-1.57– -0.12) | 0.54 (0.33– 0.90) | 0.22 (0.08– 0.58) | 0.22 (0.08– 0.58) | -2.20 (-3.25– -0.66) | 0.22 (0.08– 0.58) | 0.36 (0.24– 0.54) | 0.36 (0.24– 0.54) | -1.45 (-1.99– -0.83) | 0.37 (0.25–0.55) |
| Immune system disorders | 0.38 (0.26– 0.56) | 0.38 (0.26– 0.56) | -1.38 (-1.90– -0.79) | 0.38 (0.26– 0.56) | 0.24 (0.13– 0.44) | 0.24 (0.14– 0.44) | -2.03 (-2.77– -1.10) | 0.25 (0.14– 0.44) | 0.45 (0.36– 0.57) | 0.45 (0.36– 0.57) | -1.13 (-1.45– -0.78) | 0.46 (0.36–0.58) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.58 (0.52– 0.65) | 0.60 (0.54– 0.66) | -0.74 (-0.90– -0.58) | 0.60 (0.54– 0.67) | 0.39 (0.33– 0.45) | 0.40 (0.34– 0.47) | -1.31 (-1.55– -1.07) | 0.40 (0.34– 0.47) | 0.84 (0.79– 0.90) | 0.85 (0.80– 0.90) | -0.23 (-0.32– -0.14) | 0.85 (0.80–0.91) |
| Psychiatric disorders | 0.60 (0.53– 0.69) | 0.61 (0.54– 0.70) | -0.70 (-0.89– -0.51) | 0.61 (0.54– 0.70) | 0.38 (0.31– 0.46) | 0.39 (0.32– 0.47) | -1.36 (-1.64– -1.05) | 0.39 (0.32– 0.48) | 0.33 (0.30– 0.37) | 0.34 (0.30– 0.38) | -1.53 (-1.70– -1.36) | 0.35 (0.31–0.39) |
| Respiratory, thoracic and mediastinal disorders | 0.54 (0.48– 0.60) | 0.55 (0.49– 0.62) | -0.85 (-1.02– -0.68) | 0.55 (0.49– 0.62) | 0.47 (0.40– 0.55) | 0.48 (0.42– 0.56) | -1.04 (-1.26– -0.81) | 0.49 (0.42– 0.57) | 0.83 (0.78– 0.89) | 0.84 (0.79– 0.89) | -0.24 (-0.34– -0.15) | 0.84 (0.79–0.90) |
| Congenital, familial and genetic disorders | 1.58 (1.01– 2.46) | 1.58 (1.01– 2.45) | 0.65 (-0.03– 1.24) | 1.57 (1.01– 2.44) | 0.12 (0.02– 0.84) | 0.12 (0.02– 0.84) | -3.08 (-4.28– -0.20) | 0.12 (0.02– 0.84) | 0.20 (0.09– 0.44) | 0.20 (0.09– 0.44) | -2.31 (-3.23– -1.04) | 0.20 (0.09–0.45) |

**Table 4** (continued)

| System organ class | Tucatinib | | | | Neratinib | | | | Lapatinib | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) | ROR (95%CI) | PRR (95%CI) | IC (95%CI) | EBGM (95%CI) |
| Surgical and medical procedures | 4.16 (3.73– 4.65) | 4.05 (3.64– 4.51) | 1.98 (1.80– 2.13) | 3.94 (3.53– 4.40) | 3.26 (2.80– 3.79) | 3.20 (2.76– 3.70) | 1.66 (1.42– 1.86) | 3.15 (2.71– 3.66) | 1.22 (1.07– 1.39) | 1.22 (1.06– 1.39) | 0.27 (0.08– 0.47) | 1.21 (1.06–1.38) |
| Musculoskeletal and connective tissue disorders | 0.63 (0.56– 0.70) | 0.64 (0.58– 0.71) | -0.64 (-0.79– -0.48) | 0.64 (0.58– 0.72) | 0.52 (0.45– 0.60) | 0.53 (0.47– 0.61) | -0.90 (-1.10– -0.69) | 0.54 (0.47– 0.62) | 0.46 (0.43– 0.50) | 0.48 (0.44– 0.52) | -1.05 (-1.16– -0.93) | 0.48 (0.45–0.52) |
| Injury, poisoning and procedural complications | 1.27 (1.16– 1.38) | 1.25 (1.15– 1.36) | 0.32 (0.19– 0.45) | 1.25 (1.15– 1.36) | 1.90 (1.73– 2.08) | 1.82 (1.68– 1.98) | 0.86 (0.73– 0.99) | 1.81 (1.66– 1.98) | 0.48 (0.44– 0.52) | 0.49 (0.45– 0.54) | -1.01 (-1.13– -0.88) | 0.50 (0.46–0.54) |
| Nervous system disorders | 1.51 (1.41– 1.62) | 1.47 (1.37– 1.56) | 0.54 (0.44– 0.65) | 1.46 (1.36– 1.56) | 0.91 (0.82– 1.01) | 0.91 (0.83– 1.01) | -0.13 (-0.28– 0.03) | 0.92 (0.82– 1.02) | 0.85 (0.80– 0.90) | 0.86 (0.81– 0.91) | -0.21 (-0.30– -0.13) | 0.86 (0.81–0.91) |
| Investigations | 0.98 (0.91– 1.05) | 0.98 (0.92– 1.05) | -0.03 (-0.13– 0.08) | 0.98 (0.91– 1.05) | 0.52 (0.47– 0.59) | 0.55 (0.49– 0.61) | -0.87 (-1.03– -0.70) | 0.55 (0.49– 0.62) | 0.66 (0.62– 0.70) | 0.68 (0.64– 0.71) | -0.55 (-0.63– -0.47) | 0.68 (0.65–0.72) |
| Infections and infestations | 0.79 (0.71– 0.88) | 0.80 (0.72– 0.89) | -0.32 (-0.48– -0.16) | 0.80 (0.72– 0.89) | 0.75 (0.65– 0.86) | 0.75 (0.66– 0.86) | -0.40 (-0.60– -0.20) | 0.76 (0.66– 0.87) | 1.04 (0.97– 1.11) | 1.04 (0.98– 1.10) | 0.05 (-0.04– 0.14) | 1.04 (0.97–1.10) |
| Hepatobiliary disorders | 0.88 (0.74– 1.05) | 0.89 (0.75– 1.05) | -0.17 (-0.43– 0.08) | 0.89 (0.75– 1.05) | 0.35 (0.25– 0.49) | 0.35 (0.25– 0.49) | -1.49 (-1.95– -0.99) | 0.35 (0.25– 0.49) | 1.31 (1.19– 1.44) | 1.30 (1.19– 1.43) | 0.37 (0.23– 0.51) | 1.29 (1.18–1.42) |
| Ear and labyrinth disorders | 0.69 (0.46– 1.04) | 0.69 (0.46– 1.04) | -0.54 (-1.11– 0.07) | 0.69 (0.46– 1.04) | 0.45 (0.24– 0.84) | 0.45 (0.24– 0.84) | -1.14 (-1.94– -0.20) | 0.45 (0.24– 0.84) | 0.61 (0.46– 0.81) | 0.61 (0.46– 0.81) | -0.71 (-1.11– -0.28) | 0.61 (0.46–0.82) |
| Metabolism and nutrition disorders | 1.48 (1.34– 1.65) | 1.46 (1.33– 1.62) | 0.54 (0.39– 0.69) | 1.46 (1.32– 1.62) | 2.02 (1.81– 2.26) | 1.97 (1.77– 2.19) | 0.97 (0.80– 1.13) | 1.96 (1.75– 2.19) | 1.45 (1.35– 1.55) | 1.43 (1.34– 1.53) | 0.50 (0.40– 0.60) | 1.42 (1.32–1.52) |
| Product issues | 0.81 (0.51– 1.29) | 0.81 (0.51– 1.29) | -0.30 (-0.95– 0.38) | 0.81 (0.51– 1.29) | 0.27 (0.10– 0.72) | 0.27 (0.10– 0.72) | -1.88 (-2.94– -0.36) | 0.27 (0.10– 0.73) | 0.71 (0.52– 0.98) | 0.71 (0.52– 0.98) | -0.48 (-0.94– -0.01) | 0.72 (0.52–0.99) |

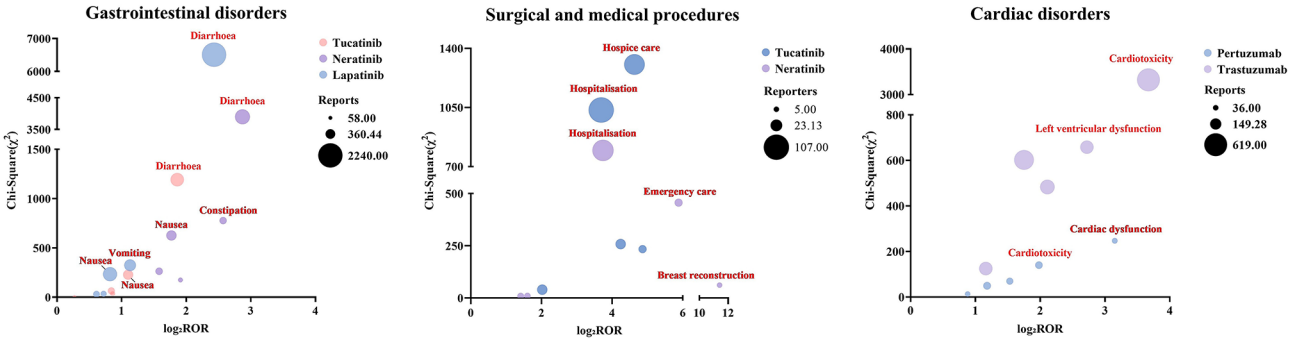



**Fig. 7** Comparison of PT signal intensity in SOCs associated with three anti-HER-2 agents

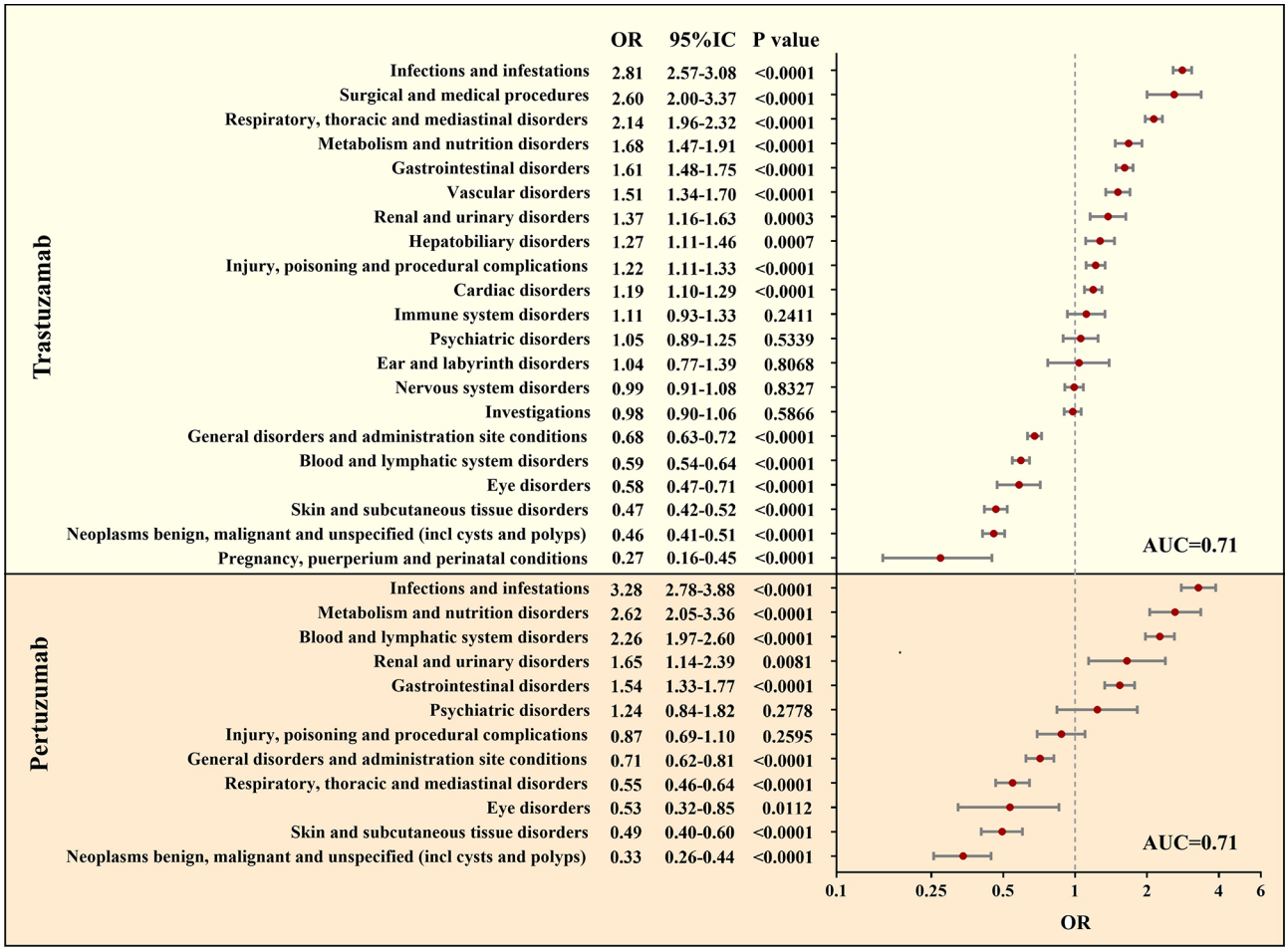



**Fig. 8** Regression analysis of the risk of hospitalization due to serious adverse events associated with mAb

for treating HER-2-positive BC. Trastuzumab has been widely utilized since its approval in the United States in 1998 and in Europe in 2000 [32]. The FDA approved pertuzumab as a standard treatment for HER-2-positive metastatic breast cancer in 2012 [33]. It is also the first agent in oncology to receive accelerated FDA approval in the neoadjuvant setting. T-DM1 and T-DXd are ADCs, and both consist of a humanized anti-HER-2 monoclonal antibody linked to a potent cytotoxic payload [34–36]. T-DXd was granted accelerated approval in the USA on December 20, 2019 for the treatment of adult patients with unresectable or metastatic HER-2-positive breast cancer who had received two or more prior anti-HER-2-based regimens in the metastatic setting [37]. In February 2013, the US FDA granted marketing approval for T-DM1 [38], which is indicated as a single agent for the treatment of patients with HER-2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, either

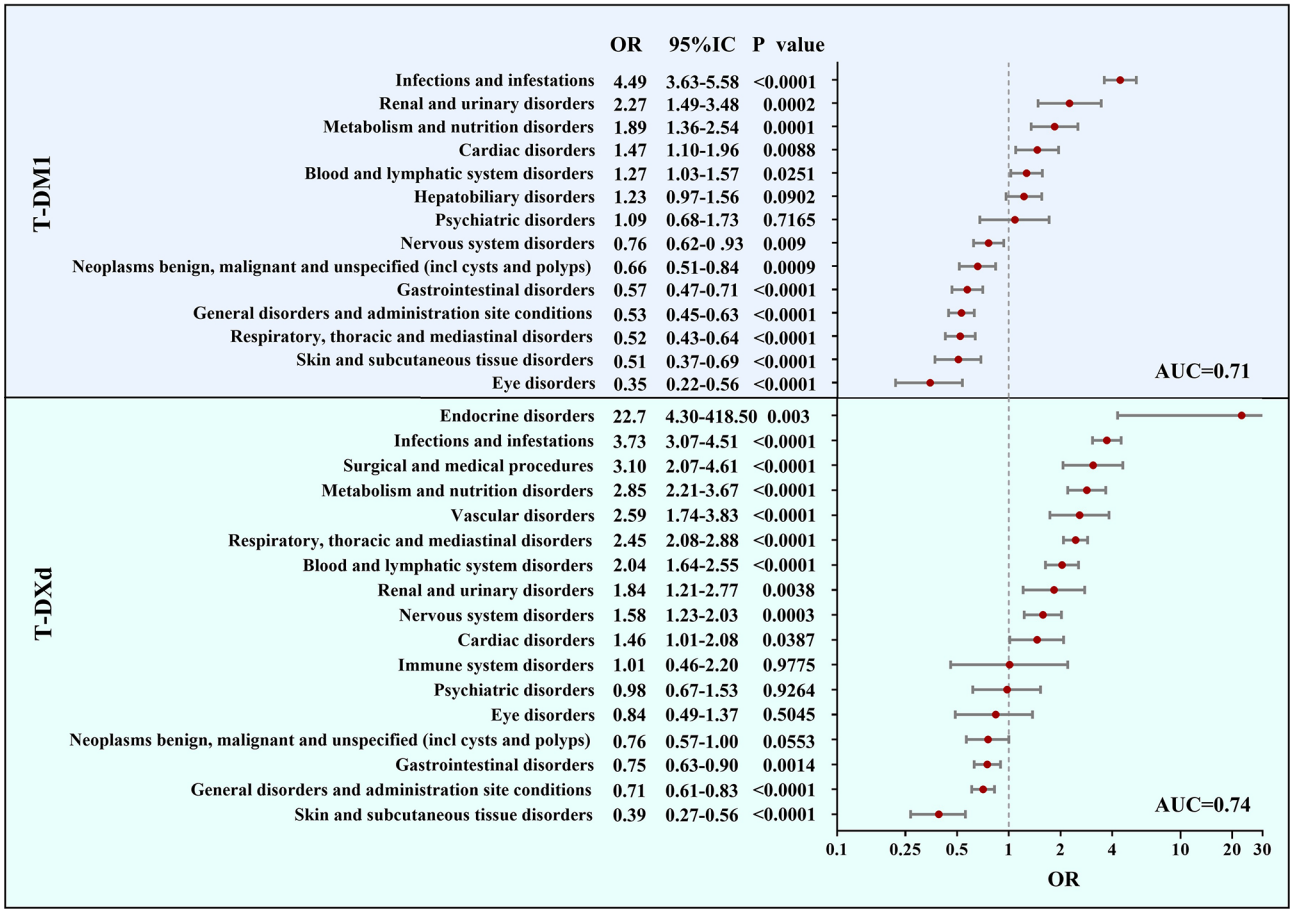



**Fig. 9** Regression analysis of the risk of hospitalization due to serious adverse events associated with ADC drugs

separately or in combination [39]. Lapatinib, an oral dual tyrosine kinase inhibitor, blocks HER-1 and HER-2 tyrosine kinase activity by binding to the ATP-binding site of the receptor's intracellular domain, resulting in the inhibition of tumor cell growth [40]. Lapatinib was first approved in 2007 by the FDA and in 2008 by the EMEA for its combined use with capecitabine in patients with advanced HER-2-positive breast cancer after progression upon therapy with anthracyclines, taxanes, and trastuzumab [39]. Tucatinib is a small-molecule drug that was approved in April 2020 by the US FDA for combination therapy with trastuzumab and capecitabine for the treatment of adult patients with advanced, unresectable, or metastatic HER-2-positive breast cancer [41]. Neratinib is an oral, small-molecule, panhuman TKI approved by the US Food and Drug Administration (FDA) in 2017 [42–45] for the extended adjuvant treatment of adults with early-stage HER-2 overexpressed/amplified breast cancer to follow adjuvant trastuzumab-based therapy in the USA [46].

In this study, trastuzumab had the highest number of reported adverse events, probably because it has been on the market for the longest time. In contrast, fewer adverse events have occurred with pertuzumab since its introduction. Similarly, the proportion of patients who died with adverse events associated with trastuzumab (12.03%) was greater than that associated with pertuzumab (9.38%). Although T-DXd has been on the market for a short time, the number of reported adverse events is high. The mortality of patients with adverse events associated with T-DXd (23.86%) was greater than that associated with T-DM1 (14.81%). The mortality of T-DXd was also the highest among all seven drugs (Fig. 3). Our data are consistent with those of previous studies. One study reported that the proportion of fatal outcomes with T-DXd was nearly twice as high as that with T-DM1 [47]. This may be related to the inherent nature of ADC drugs, in which T-DXd has a uniquely high drug-to-antibody ratio of approximately 8, whereas the T-DM1 is 3.5 [35, 36]. According to data from the last 5 years, although lapatinib was put on the market earlier, the incidence of adverse reactions is relatively low compared with that of the other two classes of drugs. Since TKI drugs are frequently administered in combination with other medications, and our study focused solely on the adverse reactions associated with the use of TKI

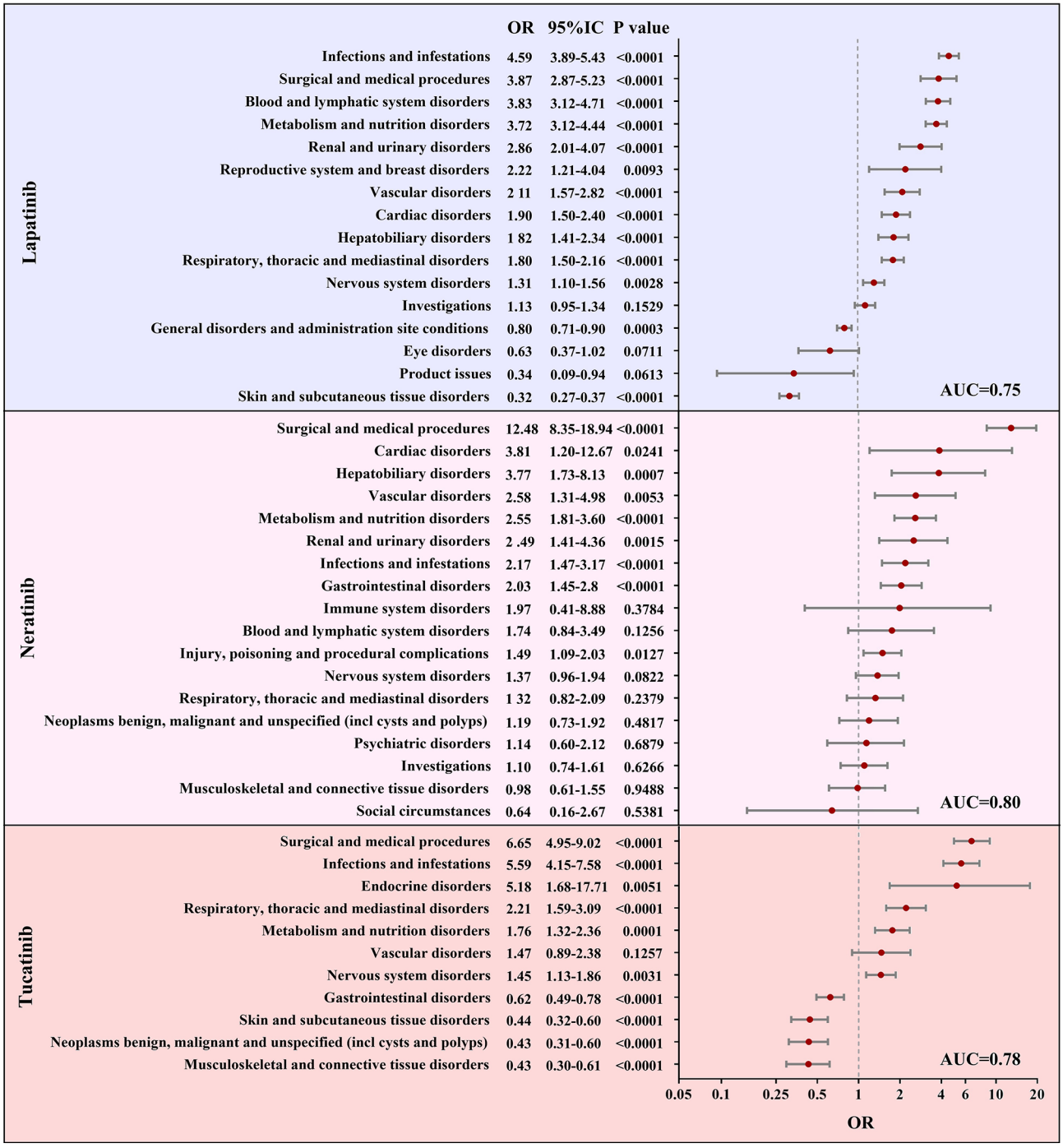



**Fig. 10** Regression analysis of the risk of hospitalization due to serious adverse events associated with TKI drugs

drugs as monotherapy, the findings are subject to certain limitations.

To analyze the signal strength of adverse drug reactions under different SOCs, we used disproportionation analysis to evaluate the adverse drug reaction signals of three classes of drugs of 27 SOCs. Trastuzumab and pertuzumab had the strongest ADR signals associated with "cardiac disorders". In particular, the ROR of trastuzumab was 3.51 (95% CI: 3.40–3.63), and the PRR was 3.34 (95% CI: 3.24–3.45). Both the IC and EBGM also showed significant ADR signals. Our results indicate that tratuzumab (ROR: 12.71, $\chi^2$: 3321.87) was associated with a greater risk of cardiotoxicity than pertuzumab (ROR: 3.93, $\chi^2$: 140.02). Left ventricular dysfunction (ROR: 6.57, $\chi^2$: 658.17) is second only to cardiotoxicity in tratuzumab. Compared with other PTs, pertuzumab had the highest

risk of cardiac dysfunction (ROR: 8.89, $\chi^2$: 247.00). Many studies have shown that cardiac toxicity, presenting as cardiac failure, is associated with trastuzumab therapy and its adverse cardiac reaction, which is also the most significant specific adverse event during treatment [48, 49]. Congestive heart failure is the most severe manifestation, while asymptomatic left ventricular ejection fraction decline is more prevalent among patients [49–51]. This is also consistent with our research conclusion. Therefore, during the treatment of breast cancer patients with pertuzumab, clinicians and pharmacists should pay more attention to adverse cardiac toxicity reactions and provide patients with early intervention and treatment. Early studies reported that patients have adverse reactions to diseases of the Blood and lymphatic system, especially neutropenia, during treatment with pertuzumab [52]. However, in our study, the SOCs of "blood and lymphatic system disorders" and "immune system disorders" also presented significant ADR signals with pertuzumab. In addition, trastuzumab also showed a significant ADR signal in "pregnancy, puerperium and perinatal conditions", in addition to its considerable ADR signal in "cardiac disorders". Studies have been conducted in that trastuzumab transfer through the placenta has been observed during the early (days 20–50 of gestation) and late (days 120–150 of gestation) pregnancy fetal complications [53]. And regarding trastuzumab administration during pregnancy, trastuzumab may mediate the reduction of amniotic fluid or some fetal complications [54].

Among the three types of drugs, ADC drugs have relatively more SOCs with significant adverse reaction signals. Hepatotoxicity is a serious adverse event associated with T-DM1 therapy, and it is dependent on the dose [55]. In this study, the results revealed that the strongest signals of T-DM1 associated with SOC is "hepatobiliary disorders". The ROR of T-DM1 was 3.09 (95% CI: 2.82–3.40), and the PRR was 3.00 (95% CI: 2.74–3.28). Some researchers have reported that TE-related hepatotoxicity leads to systemic changes in liver structure/function with resultant pathological changes in the portal venous system, such as portal hypertension, splenomegaly, esophageal varices, spider nevus and splenomegaly induced hypersplenism, which manifests as thrombocytopenia. These changes may be triggered mostly by hepatic nodular regenerative hyperplasia and/or hepatic cirrhosis [19, 56, 57]. T-DXd had a significant ADR signal in "respiratory, thoracic and mediastinal disorders" and "injury, poisoning and procedural complications". In previous studies, adverse reactions, including nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough and thrombocytopenia interstitial lung disease, pneumonia, cellulitis, hypokalemia, and intestinal obstruction, occurred in patients with unresectable or metastatic HER-2-positive breast cancer receiving T-DXd [40]. The results of this study showed that the respiratory system is the most significant SOC for the occurrence of adverse reactions during T-DXd treatment, which is consistent with previously reported conclusions. Therefore, changes in liver function and the respiratory system should be specifically monitored and managed during T-DM1 and T-DXd use in breast cancer patients to reduce the incidence of complications in cancer patients during treatment.

We found that all three TKI drugs had obvious ADR signals in "gastrointestinal diseases", among which neratinib had the strongest signal, followed by lapatinib. Studies have shown that gastrointestinal toxicity, such as diarrhea, remains the most common adverse event associated with neratinib [58, 59]. The results of this study also revealed that diarrhea is the riskiest and most frequently reported adverse event associated with TKI drugs in the SOC of patients with gastrointestinal diseases. Therefore, health care professionals should advise patients to recommend fluid and electrolyte supplementation as needed. In addition, the significant ADR signal in Surgical and medical procedures of neratinib and tucatinib may be caused by the characteristics of breast cancer treatment, such as the performance of surgical treatment (such as breast reconstruction) or the replacement of other chemotherapy regimens due to drug resistance and cancer progression. Moreover, we should pay attention to the adverse reactions associated with neratinib-related metabolic and nutritional disorders. Studies have also identified the AEs of Metabolism and nutritional disorders, such as hypokalemia, weight decrease [60], decreased appetite, and dehydration [61].

To explore factors associated with an increased risk of patient hospitalization, multivariate logistic regression analysis was conducted on 27 SOCs for which signals were detected. The results revealed that "infections and infestations", "metabolism and nutrition disorders", "renal and urinary disorders" and "gastrointestinal disorders" were the four factors strongly associated with hospitalization or prolonged hospital stay in the course of treatment with mAb agents. Moreover, "infections and infestations", "renal and urinary disorders", "metabolism and nutrition disorders", "cardiac disorders" and "blood and lymphatic system disorders" were the five factors associated with the highest risk of prolonged hospital stay due to ADC agents. In comparison, the safety of tucatinib among TKI drugs is greater than that of other drugs. The cases for lapatinib and neratinib were more complicated. These findings suggest that physicians and clinical pharmacists should inform patients about the potential occurrence of these SAEs in advance. It is essential to take preventive measures, promptly identify SAEs, and implement appropriate interventions to minimize patient harm.

## Conclusion and limitations

Based on the FAERS database, we assessed and compared the adverse effects of three classes of anti-HER-2 targeted drugs for the treatment of HER-2-related breast cancer. In general, from the perspective of the effects of the three classes of drugs on the various body systems of patients, we should focus on mAb-associated cardiac disorders, ADC-associated hepatobiliary disorders, respiratory, thoracic and mediastinal disorders, and TKI-associated gastrointestinal disorders. Our study provides valuable evidence for early clinical intervention and identification of the risk of adverse reactions associated with anti-HER-2 drugs. Furthermore, this study has certain guiding significance for the formulation of treatment plans and drug selection for HER-2-positive breast cancer patients by clinicians.

Although this study is based on a large sample of real-world data, it has certain limitations. The FAERS database is a spontaneous reporting system. Due to its own limitations, there are phenomena such as underreporting, re-reporting, and incomplete case information. Because most of the FAERS data were from the United States, the results of the study may be biased from the actual situation in other countries. Furthermore, although we have set certain criteria for the inclusion of patients, we cannot rule out the possibility that patients may have multiple complications and other complex physical conditions. Clinically, many patients tend to adopt the treatment approach of combining multiple drugs. However, this study only analyzed and evaluated the adverse events and safety signals associated with three classes of anti-HER-2 drugs used in HER-2 breast cancer monotherapy. In the future, we will continue to explore the safety of more combined treatments for breast cancer and the interactions among various drugs combined together.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-025-02013-w.

Supplementary Material 1

**Acknowledgements**

Jinming Han, Xiaohan Zhai: Data sorting and Writing-original draft preparation; Xufeng Tao, Yunming Li: Data analysis and Software application; Ziqi Zhao, Zhan Yu: Visualization; Deshi Dong, Shilei Yang: Investigation and Supervision; Linlin Lv: Ideas guidance and final editing.

**Author contributions**

JM. H. and XH. Z.:Writing-original main manuscript text and Data sorting; XF. T., YM. L.:Data analysis and Software application; ZQ. Z. and Z. Y.: Visualization; DS. D. and SL. Y.:Investigation and Supervision; Linlin Lv: Ideas guidance and final editing.

**Funding**

The program project of Dalian life and health field guidance. 2023C020.

**Data availability**

No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval and consent to participate**

Not applicable. This study is a medical research paper using a public database and it does not involve ethical issues.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

Received: 27 November 2024 / Accepted: 29 March 2025
Published online: 09 April 2025

**References**

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024[J]. Cancer J Clin. 2024;74(1):12–49.
2. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours[J]. Nature. 2000;406(6797):747–52.
3. Johnson KS, Conant EF, Soo MS. Molecular subtypes of breast cancer: A review for breast Radiologists[J]. J Breast Imaging. 2021;3(1):12–24.
4. Al-thoubaity FK. Molecular classification of breast cancer: A retrospective cohort study[J]. Annals of medicine and surgery (2012), 2020, 49: 44–48.
5. Ravdin PM, Chamness GC. The c-erbB-2 proto-oncogene as a prognostic and predictive marker in breast cancer: a paradigm for the development of other macromolecular markers–a review[J]. Gene. 1995;159(1):19–27.
6. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer[J]. Volume 244. Science (New York, NY); 1989. pp. 707–12. 4905.
7. Stanowicka-grada M, Senkus E. Anti-HER2 drugs for the treatment of advanced HER2 positive breast Cancer[J]. Curr Treat Options Oncol. 2023;24(11):1633–50.
8. Eiger D, Franzoi MA, Pondé N et al. Cardiotoxicity of trastuzumab given for 12 months compared to shorter treatment periods: a systematic review and meta-analysis of six clinical trials[J]. ESMO Open, 2020, 5(1).
9. Sawaki M, Taira N, Uemura Y, et al. Randomized controlled trial of trastuzumab with or without chemotherapy for HER2-Positive early breast cancer in older Patients[J]. J Clin Oncology: Official J Am Soc Clin Oncol. 2020;38(32):3743–52.
10. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study[J]. Lancet Oncol. 2020;21(4):519–30.
11. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, Pertuzumab, and chemotherapy versus trastuzumab emtansine plus Pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial[J]. Lancet Oncol. 2018;19(1):115–26.
12. Von Minckwitz G, Procter M, De Azambuja E, et al. Adjuvant Pertuzumab and trastuzumab in early HER2-Positive breast Cancer[J]. N Engl J Med. 2017;377(2):122–31.
13. Gianni L, Pienkowski T, IM Y H, et al. 5-year analysis of neoadjuvant Pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial[J]. Lancet Oncol. 2016;17(6):791–800.
14. Hackshaw MD, Danysh HE, Singh J, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer[J]. Breast Cancer Res Treat. 2020;183(1):23–39.
15. Paech F, Bouitbir J, Krähenbühl S. Hepatocellular toxicity associated with tyrosine kinase inhibitors: mitochondrial damage and Inhibition of Glycolysis[J]. Front Pharmacol. 2017;8:367.
16. Li Y, Gong C, Lu Q, et al. Real-World data of triplet combination of trastuzumab, lapatinib, and chemotherapy in HER2-Positive metastatic breast cancer: A multicenter retrospective Study[J]. Front Oncol. 2020;10:271.

17. Ma P, Pan X, Liu R, et al. Ocular adverse events associated with anti-VEGF therapy: A pharmacovigilance study of the FDA adverse event reporting system (FAERS)[J]. Front Pharmacol. 2022;13:1017889.
18. Liu J, Xie YM, Gai GZ, et al. [Application analysis of adverse drug reaction terminology WHOART and MedDRA][J]. Zhongguo Zhong Yao Za zhi = zhongguo Zhongyao Zazhi = China. J Chin Materia Med. 2015;40(24):4728–33.
19. Ma P, Tian H, SHI Q, et al. High risks adverse events associated with trastuzumab emtansine and trastuzumab Deruxtecan for the treatment of HER2-positive/mutated malignancies: a pharmacovigilance study based on the FAERS database[J]. Exp Opin Drug Saf. 2023;22(8):685–96.
20. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting[J]. Pharmacoepidemiol Drug Saf. 2009;18(6):427–36.
21. Subeesh V, Maheswari E, SINGH H, et al. Novel adverse events of lloperidone: A disproportionality analysis in US food and drug administration adverse event reporting system (FAERS) Database[J]. Curr Drug Saf. 2019;14(1):21–6.
22. Szarfman A, Machado SG, O'neill R T. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database[J]. Drug Saf. 2002;25(6):381–92.
23. Bate A, Lindquist M, Edwards IR, et al. A bayesian neural network method for adverse drug reaction signal generation[J]. Eur J Clin Pharmacol. 1998;54(4):315–21.
24. Omar NE, Fahmy Soliman AI, Eshra M, et al. Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA adverse event reporting system (FAERS)[J]. ESMO Open. 2021;6(6):100315.
25. Jiao XF, Li HL, Jiao XY, et al. Ovary and uterus related adverse events associated with Statin use: an analysis of the FDA adverse event reporting System[J]. Sci Rep. 2020;10(1):11955.
26. Tian X, Zheng S, Wang J, et al. Cardiac disorder-related adverse events for Aryl hydrocarbon receptor agonists: a safety review[J]. Exp Opin Drug Saf. 2022;21(12):1505–10.
27. Li X, Zhang L, Hu S, et al. Postmarketing safety of sacituzumab Govitecan: A pharmacovigilance study based on the FDA adverse event reporting System[J]. Clin Pharmacol Ther. 2024;115(2):256–68.
28. Smolarz B, Nowak AZ, Romanowicz H. Breast Cancer-Epidemiology, classification, pathogenesis and treatment (Review of Literature)[J]. Cancers, 2022, 14(10).
29. Lv L, Zhao B, Kang J, et al. Trend of disease burden and risk factors of breast cancer in developing countries and territories, from 1990 to 2019: results from the global burden of disease study 2019[J]. Front Public Health. 2022;10:1078191.
30. Nardin S, Mora E, Varughese FM, et al. Breast cancer survivorship, quality of life, and late Toxicities[J]. Front Oncol. 2020;10:864.
31. Collaborative group on hormonal factors in breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies[J]. Lancet Oncol. 2012;13(11):1141–51.
32. Luo X, Wang N, Xing Y, et al. Pharmacokinetics of trastuzumab and its efficacy and safety in HER2-positive cancer patients[J]. Cancer Chemother Pharmacol. 2024;94(5):721–32.
33. Gerratana L, Bonotto M, Bozza C, et al. Pertuzumab and breast cancer: another piece in the anti-HER2 puzzle[J]. Expert Opin Biol Ther. 2017;17(3):365–74.
34. Nicolò E, Zagami P. Antibody-drug conjugates in breast cancer: the chemotherapy of the future?[J]. Curr Opin Oncol. 2020;32(5):494–502.
35. Barok M, Joensuu H, Isola J. Trastuzumab Emtansine: mechanisms of action and drug resistance[J]. Breast cancer Research: BCR. 2014;16(2):209.
36. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, A novel HER2-Targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1[J]. Clin cancer Research: Official J Am Association Cancer Res. 2016;22(20):5097–108.
37. Keam SJ. Trastuzumab Deruxtecan: first Approval[J]. Drugs. 2020;80(5):501–8.
38. Ballantyne A, Dhillon S. Trastuzumab Emtansine: first global approval[J]. Drugs. 2013;73(7):755–65.
39. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer[J]. N Engl J Med. 2006;355(26):2733–43.
40. Voigtlaender M, schneider-merck T, Trepel M. Lapatinib[J]. Recent results in cancer research fortschritte der krebsforschung progres Dans Les recherches Sur Le cancer, 2018, 211: 19–44.
41. Shah M, Wedam S, Cheng J, et al. FDA approval summary: Tucatinib for the treatment of patients with advanced or metastatic HER2-positive breast Cancer[J]. Clin cancer Research: Official J Am Association Cancer Res. 2021;27(5):1220–6.
42. Dhillon S. Neratinib in Early-Stage breast cancer: A profile of its use in the EU[J]. Clin Drug Investig. 2019;39(2):221–9.
43. Iancu G, Serban D, Badiu CD, et al. Tyrosine kinase inhibitors in breast cancer (Review)[J]. Experimental Therapeutic Med. 2022;23(2):114.
44. López-Tarruella S, Jerez Y, Márquez-Rodas I, et al. Neratinib (HKI-272) in the treatment of breast cancer[J]. Future Oncol (London England). 2012;8(6):671–81.
45. Nasrazadani A, Brufsky A. Neratinib: the emergence of a new player in the management of HER2 + breast cancer brain metastasis[J]. Future Oncol (London England). 2020;16(7):247–54.
46. Singh H, Walker AJ, Amiri-kordestani L, et al. U.S. Food and drug administration approval: neratinib for the extended adjuvant treatment of Early-Stage HER2-Positive breast Cancer[J]. Clin cancer Research: Official J Am Association Cancer Res. 2018;24(15):3486–91.
47. Liu F, Yin G, Xue S, et al. Adverse event profile differences between trastuzumab emtansine and trastuzumab Deruxtecan: A Real-world, pharmacovigilance Study[J]. J Cancer. 2023;14(17):3275–84.
48. Huszno J, Leś D, Sarzyczny-Słota D, et al. Cardiac side effects of trastuzumab in breast cancer patients - single centere experiences[J]. Contemp Oncol (Poznan Poland). 2013;17(2):190–5.
49. Lin M, Xiong W, Wang S, et al. The research progress of Trastuzumab-Induced cardiotoxicity in HER-2-Positive breast cancer Treatment[J]. Front Cardiovasc Med. 2021;8:821663.
50. Safran H, Dipetrillo T, Nadeem A, et al. Trastuzumab, Paclitaxel, cisplatin, and radiation for adenocarcinoma of the esophagus: a phase I study[J]. Cancer Invest. 2004;22(5):670–7.
51. Nemeth BT, Varga ZV, Wu WJ, et al. Trastuzumab cardiotoxicity: from clinical trials to experimental studies[J]. Br J Pharmacol. 2017;174(21):3727–48.
52. Nordvig J, Aagaard T, Daugaard G, et al. Febrile neutropenia and Long-term risk of infection among patients treated with chemotherapy for malignant Diseases[J]. Open Forum Infect Dis. 2018;5(10):ofy255.
53. Andrikopoulou A, Apostolidou K, Chatzinikolaou S, et al. Trastuzumab administration during pregnancy: an update[J]. BMC Cancer. 2021;21(1):463.
54. Xia LY, Hu QL, Zhou Q. Use of trastuzumab in treating breast cancer during pregnancy: a systematic review and meta-analysis[J]. BMC Womens Health. 2021;21(1):169.
55. Yan H, Endo Y, Shen Y, et al. Ado-Trastuzumab emtansine targets hepatocytes via human epidermal growth factor receptor 2 to induce Hepatotoxicity[J]. Mol Cancer Ther. 2016;15(3):480–90.
56. Morris-Stiff G, White AD, Gomez D, et al. Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases[J]. Eur J Surg Oncology: J Eur Soc Surg Oncol Br Association Surg Oncol. 2014;40(8):1016–20.
57. Milam P, Berger M, Ramaswamy B, et al. Spider telangiectases and palmar erythema as harbingers of structural liver changes in three breast cancer patients on Ado-trastuzumab Emtansine[J]. J Clin Aesthetic Dermatol. 2019;12(7):23–6.
58. Deeks ED, Neratinib. First global Approval[J]. Drugs. 2017;77(15):1695–704.
59. Jankowitz RC, Abraham J, Tan AR, et al. Safety and efficacy of neratinib in combination with weekly Paclitaxel and trastuzumab in women with metastatic HER2–positive breast cancer: an NSABP foundation research program phase I study[J]. Cancer Chemother Pharmacol. 2013;72(6):1205–12.
60. Guo L, Shao W, Zhou C et al. Neratinib for HER2-positive breast cancer with an overlooked option[J]. Molecular medicine (Cambridge, Mass), 2023, 29(1): 134.
61. Fan Y, Wu T, Xu P, et al. Neratinib safety evaluation: real-world adverse event analysis from the FAERS database[J]. Front Pharmacol. 2024;15:1425171.


## Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.